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(54) Titre : UTILISATION DE LA NALBUPHINE POUR LE TRAITEMENT DE LA DYSKINESIE
(54) Title: USE OF NALBUPHINE FOR TREATING DYSKINESIA

(57) Abrégé/Abstract:
Provided is a use of a therapeutically effective amount of Nalbuphine or a pharmaceutically acceptable salt thereof for treating or mitigating levodopa-induced dyskinesia in a subject diagnosed with Parkinson's disease. In addition, a use of a therapeutically effective amount of a prodrug of Nalbuphine selected from the benzoate ester of Nalbuphine, the sebacoyl diester of Nalbuphine or a pegylated derivative of Nalbuphine for treating or mitigating dyskinesias associated with Tourette's syndrome and Huntington's disease in a subject in need thereof is provided.

ABSTRACT

Provided is a use of a therapeutically effective amount of Nalbuphine or a pharmaceutically acceptable salt thereof for treating or mitigating levodopa-induced dyskinesia in a subject diagnosed with Parkinson's disease. In addition, a use of a therapeutically effective amount of a prodrug of Nalbuphine selected from the benzoate ester of Nalbuphine, the sebacoyl diester of Nalbuphine or a pegylated derivative of Nalbuphine for treating or mitigating dyskinesias associated with Tourette's syndrome and Huntington's disease in a subject in need thereof is provided.

USE OF NALBUPHINE FOR TREATING DYSKINESIA

FIELD OF THE INVENTION

The present invention relates to a method of treatment for dyskinesias, including levodopa-induced dyskinesias (LID) in Parkinson's disease, and the dyskinesias associated with Tourette's syndrome, tardive dyskinesia and Huntington's disease.

BACKGROUND OF THE INVENTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder afflicting 1.5 million individuals in the US and 6.3 million worldwide. The incidence of PD is expected to double by the year 2040. In the US, 50,000 new cases are diagnosed per year, and 1% of the population over the age of 55 is afflicted. The annual societal cost of PD is above $25 billion in the US alone.

The most common treatment for PD is 3,4-dihydroxyphenylalanine (levodopa or L-DOPA). While it remains the most effective therapy for the motor disability caused by PD, the vast majority of patients suffering from PD eventually develop a side effect characterized by abnormal involuntary movements known as L-DOPA induced dyskinesias (LID), which substantially compounds patient disability. Thus, LID is a common, devastating complication of the most efficacious therapeutic agent for PD. Dyskinesia is a disorder characterized by the presence of involuntary movements that are often uncontrollable. These movements are often choreiform (dance-like) in appearance but can also be more jerky and abrupt. They can affect any body parts including the arms and legs, muscles of the torso, chest, pelvis, face, lips, tongue, eyelids, and neck. It can even affect respiratory muscles. Some of these movements can be strong and violent that can lead to injuries including to the cervical spine (neck). Thus, dyskinesia is a major source of disability. Therefore, although L-DOPA is the gold standard in

the management of PD, long-term treatment with L-DOPA is problematic. L-DOPA-induced dyskinesia affects 50% of treated PD patients by 5 years, and >90% by 10 years, which translates to an increase of approximately 10% per year. There are approximately 200,000 cases of LID in the US alone. Currently, amantadine (1-adamantanamine hydrochloride) is the only drug available that can modestly reduce LID, representing a deficient treatment with significant side effects of its own. Amantadine has an anti-dyskinetic effect likely due to its NMDA glutamate receptor antagonism, and it remains the only marketed agent with such a property. Several other experimental compounds targeting various transmitter systems have been tested, all with negative clinical trial outcomes. Moreover, in PD patients, LID is the main indication for the invasive and costly brain surgery known as Deep Brain Stimulation (DBS), an extreme option with the potential for serious neuropsychiatric side effects as well as the usual risks associated with invasive brain surgery. As a result, many patients are deemed poor candidates for this surgery, leaving their LID inadequately controlled.

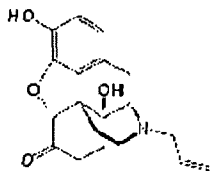
Opioid receptors and LID

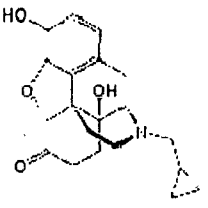
Central to the development of LID appear to be changes in neuronal networks that are modulated by glutamatergic, adenosinergic, adrenergic, dopaminergic, serotoninergic, endocannabinoid and opioid mediated neurotransmission, all of which have been characterized to be altered in disease. Of these, opioid receptor mediated neurotransmission is of particular interest as opioids are co-transmitters that modulate basal ganglia function. Through this action, opioid drugs may help blunt the negative effects of pulsatile stimulation with L-DOPA therapy that is pathogenically related to LID. In LID, precursors of endogenous opioid receptor ligands are massively upregulated, with preproenkephalin levels increased in the striatum in animal models, as well as being observed in postmortem studies of patients. Additionally, enkephalin, dynorphin and alpha-neoendorphin are elevated significantly in the dyskinetic state, but not in normal or nondyskinetic Parkinsonian state. Therefore, it has been proposed that opioid receptor antagonism may be of benefit. However, the complexity of the basal ganglia circuitry, the presence of opioid receptors both pre- and post-synaptically, and on both excitatory and inhibitory neurons, significantly compound the intricacies of the response to opioid receptor ligands that must be considered. There are three major relevant classes of opioid receptors with differential distributions in the basal ganglia and with different functions:

- Delta (δ) – Expressed predominantly in striatum and subthalamic nucleus, with lower levels in Globus Pallidus (GP) segments. These receptors regulate glutamate and acetylcholine release in the striatum.
- Kappa (κ) – Expressed in all basal ganglia regions (striatum, GPe, GPi, STN, SN) & thalamus.
- Mu (μ) – Expressed in all basal ganglia regions and thalamus.

Further complexity arises as expression of opioid receptors change in the Parkinsonian state. For example, kappa receptors are decreased in substantia nigra, and kappa and mu receptors are decreased in GPi in LID, likely secondary to alterations in opioid ligand expression. This complexity in distribution and function is probably the reason why non-selective antagonists have shown extremely varied efficacy in LID, worsening, not affecting, or ameliorating symptoms in animal models, and have not been effective in small clinical trials. Therefore, a level of specificity is believed to be required, but the precise nature of this specificity appears to be complex. The effects of more compounds can be summarized as follows:

- The μ-opioid receptor selective antagonist cyprodime significantly reduces peak-dose LID. However, the selective μ-opioid receptor antagonist ADL5510 reduces LID but with a U-shaped dose response curve
- The κ-opioid receptor selective agonist U50,488 reduces LID but worsens parkinsonism in MPTP-treated primates. However, the κ-opioid receptor selective antagonist *nor*-BNI moderates levodopa-induced hyperkinesias in the 6-hydroxydopamine-lesioned rat model.
- Lower doses of the selective δ-opioid receptor antagonist naltrindole reduce levodopa-induced rotations in hemiparkinsonian marmoset monkeys.
- Morphine (nonselective opioid receptor agonist) reduces dyskinetic movements in Parkinsonian primates and patients
- Naloxone and Naltrexone (nonselective opioid receptor antagonists) have been tested with variable effects in monkeys and humans reporting no change, increases or decreases in LID.


Naloxone


Naltrexone

Collectively, the compounds tested to date indicate potential for modulating opioid receptors, but also indicate great complexity. Even those that are efficacious at some doses may display U-shaped dose response curves as non-specificity becomes an issue such as occurs with ADL5510. Consideration of these studies indicates that the most efficacious anti-dyskinetic agent acting on the opioid receptor system would have an as yet undiscovered mixture of pharmacological actions on different opioid receptors.

Safety Considerations of Opioid Drugs

Activation of opioid receptors is achieved by a number of widely used and abused opiates such as morphine and codeine. Despite the clear beneficial effects that these compounds can have in analgesia and other indications, they can have severe addictive and sedative effects, while antagonists can precipitate withdrawal symptoms in patients on opiates. Therefore, doses relevant for LID need to be considered in light of these side effects. The major specific side effects relevant to mu-antagonists are related to the gastrointestinal tract and dysphoria, while for kappa-agonists are sedation, worsening parkinsonism and dysphoria for example.

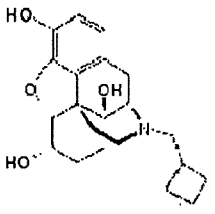
In summary, in LID there are increases in the release of opioid peptide precursors, therefore, modulation of opioid receptors is an attractive therapeutic approach. The complexity of how different opioid receptors regulate signaling at different sites within the circuitry of the basal ganglia dictates the selectivity profile that will be efficacious to modulate. The broad spectrum opioid receptor antagonists, such as Naloxone and Naltrexone, have been proposed as possible therapeutics, but have not been clinically successful. Selective agents for specific opioid receptor isoforms may offer limited benefits, but also demonstrate opposing dose-dependent effects that can substantially reduce their utility with significant dose-limiting adverse effects.

Thus, there remains a significant need for a therapeutic agent to treat L-DOPA-induced dyskinesias, since LID is a critical condition affecting a large and increasing population of PD

patients. Further, there are other orphan diseases that exhibit dyskinesias for which treatments are unavailable or inadequate; these diseases include Huntington's disease, Tourette's syndrome and tardive dyskinesia. The present invention addresses these unmet needs.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to a novel use of Nalbuphine and related compounds as a therapeutic agent to treat dyskinesias, especially L-DOPA induced dyskinesias (LID), common in PD patients. Specifically, the present invention comprises the use of Nalbuphine in the treatment of LID.



Nalbuphine

In one embodiment, the present invention relates to methods of treating or mitigating various forms of dyskinesia, including, but not limited to, LID, especially in PD patients; tardive dyskinesias; Tourette's syndrome; and Huntington's disease, comprising administering a therapeutically effective amount of a dual-action mu-opioid receptor antagonist/kappa-opioid receptor agonist to a patient in need thereof sufficient to mitigate the dyskinesia. Mitigation of dyskinesia is defined as reduced severity and/or duration of abnormal involuntary movements based on validated scales administrated by trained personnel and by patient diaries marking "on with non-troublesome dyskinesia" or "on with troublesome dyskinesia." The dual-acting agents can be selected from the group consisting of Nalbuphine, Nalorphine, Pentazocine, Butorphanol and combinations of two or more thereof, their prodrugs or related compounds. Preferably the dual-acting agent comprises Nalbuphine.

Another embodiment of the invention comprises administering a therapeutically effective amount of Nalbuphine to a subject in need thereof in a non-injectable composition comprising:

a. Nalbuphine in the form of a free-base or a pharmaceutically acceptable derivative, prodrug or salt, in an amount of at least 0.01 milligram; and

b. a pharmaceutically acceptable carrier;

where the composition is in tablet or capsule form. Preferably the Nalbuphine composition is administered orally. Preferably component a. is present in an amount of at least 0.1 mg.

In yet another embodiment of the invention, the dual-action mu-antagonist/kappa-agonist comprises Nalbuphine administered to a subject via a continuous infusion. Preferably the continuous infusion dose is at least about 0.0001 mg/kg/day.

Another embodiment of the invention is directed to a method of treating or mitigating a dyskinesia, comprising administering therapeutically effective amounts of both a mu-opioid receptor antagonist and a kappa-opioid receptor agonist to a subject in need thereof, sufficient to mitigate said dyskinesia. The agents may be administered together or separately.

A further embodiment of the invention is directed to a method of treating or mitigating a dyskinesia, comprising administering a therapeutically effective amount of a prodrug of a dual-action mu-opioid receptor antagonist/kappa-opioid receptor agonist to a subject in need thereof, sufficient to mitigate said dyskinesia. Preferably, the prodrug is a prodrug of Nalbuphine, most preferably an ester of Nalbuphine, optionally as a pharmaceutically acceptable salt.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 displays graphs of dyskinesia score over time for two Parkinsonian monkeys treated with L-DOPA with and without Nalbuphine.

Figure 2 displays a graph of dyskinesia score over time for three additional Parkinsonian monkeys treated with L-DOPA with and without Nalbuphine.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Nalbuphine – a dual mu-antagonist/kappa-agonist

Nalbuphine (Nubain) is a synthetic opioid with activity as both a mu-opioid receptor antagonist and a kappa-opioid receptor agonist. It has been used clinically since 1979 as an analgesic for moderate/severe pain including for women in labor. It is the only narcotic of its type that is not regulated under the Controlled Substances Act, an indication of its safety, with the major side effect being mild sedation at analgesic doses in a subset of people. According to our analysis, Nalbuphine has properties required to be an effective agent for LID with a safety window that makes its use viable at sub-analgesic, non-sedative doses. It exhibits activity as a

dual mu-opioid receptor antagonist and kappa-opioid receptor agonist. As such, it provides the opportunity to combine these two activities into a single, safe, therapeutic agent. Thus, Nalbuphine offers key pharmacological advantages such as fixed ratio of mu-antagonism/ kappa agonism in relevant brain compartments, regardless of dose, dosage form or stage of the disease in a particular patient. This unique characteristic results in a medical advantage – ability to treat LID without risk of exposing a patient to excessive kappa agonism which has been reported to cause severe side effects in LID patients and other relevant disease states.

Another surprising finding is that kappa agonism of Nalbuphine exerts its anti-LID efficacy without worsening parkinsonism.

Currently, Nalbuphine is administered for pain relief as an intramuscular injection, which is not necessarily a desirable route for chronic administration in LID or other chronic conditions. Due to its safety and efficacy, oral forms may be preferable. Oral formulations of Nalbuphine are disclosed in the following patents or patent publications: US 6,703,398; US 2009/0030026; EP 2402005; WO 2007/127683 and US 2009/0060871. Although these have been proven efficacious, they are not commercially viable in the field of analgesia and, thus, their further development and marketing has not been achieved. We have generated proof-of-concept data with the injectable dosage form in the primate model of PD with LID.

One embodiment of the present invention relates to the novel use of dual-action mu-opioid receptor antagonist/kappa-opioid receptor agonists, represented by Nalbuphine and related compounds, as a therapeutic agent to treat dyskinesia, especially L-DOPA induced dyskinesias (LID) common in PD patients. It is known that opioid transmission in the basal ganglia is an integral part of voluntary movement control; thus, this mechanism has been implicated in LID. Although modulation of specific opioid receptors has been proposed as a treatment for LID, the experimental agents examined to date have resulted in clinical inefficacy and unacceptable side effects. Thus, one particular embodiment of the present invention is directed to the use of a dual-action mu-opioid receptor antagonist/kappa-opioid receptor agonist agent, preferably Nalbuphine, in the treatment of LID and dyskinesias associated with other diseases such as tardive dyskinesias, Tourette's syndrome and Huntington's disease. Further, the invention is also directed to the treatment of such dyskinesias with a combination of both a mu-opioid receptor antagonist and a kappa-opioid receptor agonist. This combination of drugs may be administered

together or separately. If administered separately, various time delays between the administration of the individual dosage forms are possible, depending on the needs of the patient. If administered together, a combination of individual dosage forms may be given, or the drugs may be formulated as a single composition.

One embodiment of the present invention offers a novel method of treatment of LID and other dyskinesias using such dual-acting mu-opioid receptor antagonist/kappa-opioid receptor agonist agents, which have the advantages of possessing a low incidence of side effects, a "ceiling" for side effects, and being non-addictive. Furthermore, such dual-acting therapeutic agents have surprisingly increased efficacy compared to other strategies and address an area of medicine with major, unmet needs, *vide infra.*

In another embodiment, the present invention is directed to a method of treating or mitigating various types of dyskinesias, including, but not limited to, LID, especially in PD patients; tardive dyskinesias; Tourette's syndrome; and Huntington's disease and related diseases, comprising administering a composition comprising both a mu-opioid receptor antagonist and a kappa-opioid receptor agonist.

In another embodiment, the present invention is directed to a method of treating or mitigating various types of dyskinesias, including, but not limited to LID, especially in PD patients; tardive dyskinesias; Tourette's syndrome; and Huntington's disease and related diseases, comprising administering a composition comprising a single therapeutic agent which is active both as a mu-opioid receptor antagonist and a kappa-opioid receptor agonist. Representative of such dual-acting mu-opioid receptor antagonist/kappa-opioid receptor agonist agents is the synthetic analgesic opioid, Nalbuphine.

In another embodiment, the present invention is directed to a method of treating or mitigating dyskinesias comprising administering Nalbuphine, Nalorphine, Pentazocine, Butorphanol or a combination of two or more of these.

In a more specific embodiment, the present invention is directed to a method of treating or mitigating various types of dyskinesias in a patient in need thereof, including, but not limited to LID, especially in PD patients; tardive dyskinesias; Tourette's syndrome; and Huntington's disease, comprising administering a safe and effective amount of Nalbuphine, preferably in the dosage range of about 0.001 mg/kg to about 3 mg/kg.

In another embodiment, the present invention is directed to a method of treating or mitigating dyskinesias comprising administering to a subject in need thereof a non-injectable or injectable pharmaceutical composition comprising a combination of both a mu-opioid receptor antagonist and a kappa-opioid receptor agonist, or alternatively, comprising a dual-acting therapeutic agent possessing both mu-opioid receptor antagonist and kappa-opioid receptor agonist activities, in various administration vehicles, including but not limited to tablets, capsules, caplets, syrups, gels, suppositories, inhalable powders, inhalable aerosols, sublingual sprays, sublingual solid dosage form, patch, intranasal sprays, intranasal aerosols, injectable solutions and injectable suspensions including those delivered via minipumps and other devises capable of continuous delivery of the agent . If the pharmaceutical composition is administered by injection, the injection may be intravenous, subcutaneous, intramuscular, intraperitoneal or by other means known in the art. The present invention may be formulated by any means known in the art, including but not limited to formulation as suspensions, powders, lyophilized preparations, ocular drops, skin patches, oral soluble formulations, sprays, aerosols and the like, and may be mixed and formulated with buffers, binders, excipients, stabilizers, anti-oxidants and other agents known in the art. Administration means may include administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration and the like.

In a preferred embodiment, the present invention is directed to a method of treating or mitigating dyskinesias comprising administering to a subject in need thereof a non-injectable, pharmaceutically acceptable oral formulation comprising an active component including free-base Nalbuphine or a pharmaceutically acceptable derivative or salt of Nalbuphine, and a pharmaceutically acceptable carrier or adjuvant; and wherein the formulation is in tablet or capsule form. For the present invention, the term "derivative" means a compound derived from a drug molecule, for example Nalbuphine, which can regenerate or release the parent drug (e.g, Nalbuphine) at a target site *in vivo,* for example when acted upon by hydrolytic and/or oxidative enzymes. Such derivatives are known as "prodrugs" in the medicinal chemistry arts. Prodrugs are generally derivatives of the drug, for example esters of carboxylic acids, or conjugates with amino acids, peptides or proteins. Prodrug derivatives influence the uptake, transport, toxicity and/or metabolism properties of the parent drug.

There are known Nalbuphine prodrugs designed to improve its pharmacokinetic and pharmacodynamic profiles. For example, Nalbuphine can be modified at the phenolic hydroxyl by acylation to form esters or by alkylation to form ethers. Furthermore, Nalbuphine can be coupled to an amino acid or short peptide. Also, Nalbuphine can be modified with dicarboxylic acids themselves or dicarboxylic acid linked-amino acids or dicarboxylic acid linked-peptides. Further, Nalbuphine can be modified with a carbamate-linked amino acid or peptide. Nalbuphine can be further modified on its nitrogen atom by forming salts or N-oxides. As discussed above, Nalbuphine can be converted to ester prodrugs which increase its bioavailability. More specifically, formulation to increase Nalbuphine's bioavailability can include vegetable oils, a co-solvent, and an effective amount of a Nalbuphine ester prodrug or a pharmaceutically acceptable salt thereof, which can increase the oral bioavailability of Nalbuphine by more than 12 times, and prolong the retention time of Nalbuphine in the body, thereby maintaining a longer analgesic period, as well as reducing the analgesic cost, since Nalbuphine esters have long-acting analgesic action. For example, the bioavailability of sebacoyl di-Nalbuphine ester is improved over that of Nalbuphine itself. Nalbuphine prodrugs also include Nalbuphine covalently linked to another pharmaceutical agent, for example via an amino acid. For example, Nalbuphine can be converted into a 3-acetylsalicylate (aspirin®) derivative. Such duplex prodrugs including Nalbuphine provide a significant increase in the transdermal flux of drugs across human skin. Transdermal delivery of Nalbuphine and Nalbuphine pivalate from hydrogels by passive diffusion and ionto-phoresis *(vide infra)* has also been described. Therapeutic polymers such as polyesters and poly-amides incorporating Nalbuphine, as well as polyNalbuphine derivatives can also be prepared. Controlled release of Nalbuphine prodrugs from biodegradable *polymeric matrixes is influenced* by prodrug hydrophilicity and polymer composition.

Pharmacokinetic and pharmacodynamic properties of Nalbuphine, its pharmaceutically acceptable salts, esters or other prodrugs can be further modulated by various delivery systems. For example, biodegradable polymeric microspheres for Nalbuphine prodrug controlled delivery have been described. Further, iontophoresis and electroporation enhance the transdermal delivery of Nalbuphine (NA) and two prodrugs, Nalbuphine benzoate (NAB) and sebacoyl di-Nalbuphine ester (SDN), when applied topically as solutions or hydrogels. Mucoadhesive buccal disks also provide for novel Nalbuphine prodrug controlled delivery.

In a further embodiment of the present invention, prodrugs of mu-opioid receptor antagonists and/or kappa-opioid receptor agonists and/or other dual-action mu-antagonist/kappa-agonist compounds, and/or other therapeutic agents can be used either as individual therapeutic agents or in combination with any of the above for the treatment of dyskinesias.

The present invention represents a novel treatment option for those suffering from LID as well as other forms of dyskinesias including tardive dyskinesia, Huntington's chorea and Tourette's syndrome. Nalbuphine functions by modulating locomotion by interacting with mu-opioid receptor as an antagonist and kappa-opioid receptor as an agonist. Nalbuphine administration offers a distinct advantage in that it does not cause significant euphoric, dysphoric or sedative effects, at the doses of the present invention. Additionally, the method of the present invention does not impair cognition or respiration. Furthermore, Nalbuphine has been shown to be safe (in 30 years of clinical use as an analgesic), non-addictive at sub-analgesic doses, and having a "ceiling effect" that limits adverse effects at higher doses.

The compounds described herein can also be co-administered with other anti-dyskinetic drugs (e.g. amantadine, adenosine A2a antagonists, alpha-2 adrenergic antagonists (e.g. fipamezole)) and/or anti-Parkinson treatments (e.g. L-DOPA, dopamine agonists, monoamine oxidase (MAO) inhibitors (e.g. Safinamide), catechol-O-methyl transferase inhibitors, deep brain stimulation, etc.). Thus, a further embodiment of the invention encompasses a method of treating or mitigating a dyskinesia wherein a dual-action mu-antagonist/kappa-agonist or prodrug thereof is administered with another anti-Parkinson agent. Preferably the other anti-Parkinson agent is selected from the group consisting of L-DOPA, dopamine agonists, MAO inhibitors, COMT inhibitors, amantadine and anti-cholinergics. More preferably the other anti-Parkinson agent comprises L-DOPA. Most preferably the other anti-Parkinson agent is L-DOPA. Most preferably the dual-action mu-antagonist/kappa-agonist is Nalbuphine or a prodrug thereof, and the other anti-Parkinson agent is L-DOPA. Administration of either of the agents can be delayed by 0-12 hrs, preferably by 0-6 hours, and administration can be via the same or by a different route.

EXAMPLES

The present invention is described more fully by way of the following non-limiting examples. Modifications of these examples will be apparent to those skilled in the art. In order

to target Nalbuphine for the treatment of Levodopa-induced dyskinesias, a major need for Parkinson's disease patients, its activity is confirmed in preclinical models and those data are used to guide dosing for human clinical trials.

Example 1: Assess efficacy, safety and dosing of Nalbuphine in a primate model of L-DOPA induced dyskinesias

Studies in primates are necessary to closely replicate the human condition and are used to fine tune the dosing and efficacy prior to a human clinical trial. The primate model of Parkinson's disease is a well established model that replicates the motor manifestations of the human disease, is responsive to PD therapeutics, and develops L-dopa-induced dyskinesia. Macaque monkeys (*Macaca Fascicularis*) are used in these studies, to which MPTP (*1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine*; 0.5-0.8 mg/kg) is administered intravenously (iv) until a stable Parkinsonian state of moderate to severe degree develops. The animals are then administered oral levodopa / carbidopa (Sinemet 25/100) twice daily until stable dyskinesias are established. The response of animals to subcutaneous (SC) injections of levodopa methyl ester alone is then assessed, and the optimal dose established for each animal that results in moderate and reproducible dyskinesia. Levodopa methyl ester is routinely given with benserazide, a decarboxylase inhibitor to lessen the peripheral side effects of levodopa. Animals are then administered Nalbuphine SC, along with levodopa methyl ester plus benserazide to assess the effect of the combination on the severity and duration of dyskinesias. A minimum of 4 Nalbuphine doses and vehicle are administered in random order to ensure integrity of the studies, with the aim of finding a minimum efficacious dose and determining a viable dosing strategy for a future clinical trial. Each test dose including the vehicle is repeated 3 times. Monkeys are scored before L-DOPA administration and every 20 min interval thereafter for 3-4 hours. Tests are performed by trained observers in the morning after overnight fasting and repeated at intervals of at least 48 hr for drug washout. In addition to general clinical evaluation, a standardized scale for MPTP-treated primates to assess dyskinesias, the Klüver board test (motor task), and a scale assessing the nervous system (particularly alertness) is used. The examples described above identify efficacious doses of Nalbuphine that can be translated to human clinical trials.

Data

Macaques received iv MPTP to induce advanced Parkinsonism and were treated with chronic oral L-dopa/carbidopa to induce dyskinesia.

Example 1A: Nalbuphine was tested in two Parkinsonian monkeys with LID, at 0.1 mg/kg and 0.2 mg/kg given with 75 mg levodopa methyl ester (plus benserazide) all injected SC. Responses were evaluated with a motor disability scale for Parkinsonian monkeys including abnormal involuntary movements (PD-MDS). In both animals, dyskinesia severity was ameliorated and lasted for a shorter time when Nalbuphine was co-administered compared with levodopa administration alone (Figure 1). No sedation occurred at these doses.

Example 1B: Three Parkinsonian monkeys with LID were tested. Animals were challenged with 75 mg SC injection of L-dopa methyl ester (plus benserazide) alone or immediately following SC Nalbuphine (0.25 mg/kg or 0.5 mg/kg), and responses were evaluated with a motor disability scale for Parkinsonian monkeys including abnormal involuntary movements. Each treatment was tested 2-3 times per animal. Error bars = S.E.M. Substantial reduction in the severity and duration of dyskinesias were noted with Nalbuphine co-administration. The effect of 0.5 mg/kg was slightly more pronounced than 0.25 mg/kg suggesting a dose-response effect (Figure 2). Again, no sedation or other adverse effects were noted in these animals.

The foregoing examples and descriptions of the preferred embodiments are presented as illustrating, rather than as limiting the present invention as defined by the following claims. The present invention encompasses all variations and combinations of the features presented above, and are intended to be within the scope of the claims.

CLAIMS

What is claimed is:

1. Use of a therapeutically effective amount of Nalbuphine or a pharmaceutically acceptable salt thereof for treating or mitigating levodopa-induced dyskinesia in a subject diagnosed with Parkinson's disease.

2. Use of a therapeutically effective amount of Nalbuphine or a pharmaceutically acceptable salt thereof for treating or mitigating tardive dyskinesia in a subject in need thereof.

3. Use of a therapeutically effective amount of Nalbuphine or a pharmaceutically acceptable salt thereof for treating or mitigating dyskinesias associated with Tourette's syndrome and Huntington's disease in a subject in need thereof.

4. The use of any one of claims 1 to 3 wherein said Nalbuphine is for administration to a subject at a dose between 0.001 mg/kg and 3 mg/kg.

5. The use of any one of claims 1 to 4 wherein said Nalbuphine is in the form of a non-injectable composition comprising:

a. Nalbuphine in the form of a free-base or a pharmaceutically acceptable salt, in an amount of at least 0.01 mg; and

b. a pharmaceutically acceptable carrier;

wherein said composition is in tablet or capsule form.

6. The use of any one of claims 1 to 4 wherein said Nalbuphine is for administration to said subject in a non-injectable pharmaceutical composition for treating the dyskinesia, wherein said pharmaceutical composition is in a form selected from the group consisting of tablets, capsules, syrups, gels, suppositories, skin patches, inhalable powders, inhalable aerosols, sublingual sprays, sublingual solid dosage forms, intranasal sprays, intranasal aerosols and a medical device capable of continuous delivery of a pharmaceutical agent.

Date Reçue/Date Received 2020-07-27

7. Use of a therapeutically effective amount of a prodrug of Nalbuphine selected from the group consisting of the benzoate ester of Nalbuphine, the sebacoyl diester of Nalbuphine and a pegylated derivative of Nalbuphine for treating or mitigating levodopa-induced dyskinesia in a subject diagnosed with Parkinson's disease.

8. Use of a therapeutically effective amount of a prodrug of Nalbuphine selected from the group consisting of the benzoate ester of Nalbuphine, the sebacoyl diester of Nalbuphine and a pegylated derivative of Nalbuphine for treating or mitigating tardive dyskinesia in a subject in need thereof.

9. Use of a therapeutically effective amount of a prodrug of Nalbuphine selected from the group consisting of the benzoate ester of Nalbuphine, the sebacoyl diester of Nalbuphine and a pegylated derivative of Nalbuphine for treating or mitigating dyskinesias associated with Tourette's syndrome and Huntington's disease in a subject in need thereof.

10. The use of any one of claims 7 to 9 wherein said prodrug is an ester of Nalbuphine selected from the group consisting of the benzoate ester of Nalbuphine, and the sebacoyl diester of Nalbuphine.

11. The use of any one of claims 7 to 9 wherein said prodrug is a pharmaceutically acceptable salt of an ester of Nalbuphine selected from the group consisting of the benzoate ester of Nalbuphine and the sebacoyl diester of Nalbuphine.

12. The use of claim 1 or 7 further including the use of an anti-Parkinson agent for treating or mitigating the symptoms of Parkinson's disease.

13. The use of claim 12, wherein said anti-Parkinson agent is selected from the group consisting of L-DOPA, dopamine agonists, MAO inhibitors, COMT inhibitors, amantadine and anti-cholinergics.

14. The use of claim 12, wherein said anti-Parkinson agent is L-DOPA.

Date Reçue/Date Received 2020-07-27

15. The use of claim 12, wherein said anti-Parkinson agent is a dopamine agonist.

16. The use of claim 12, wherein said anti-Parkinson agent is a MAO inhibitor.

17. The use of claim 12, wherein said anti-Parkinson agent is a COMT inhibitor.

18. The use of claim 12, wherein said anti-Parkinson agent is amantadine.

19. The use of claim 12, wherein said anti-Parkinson agent is an anti-cholinergic.

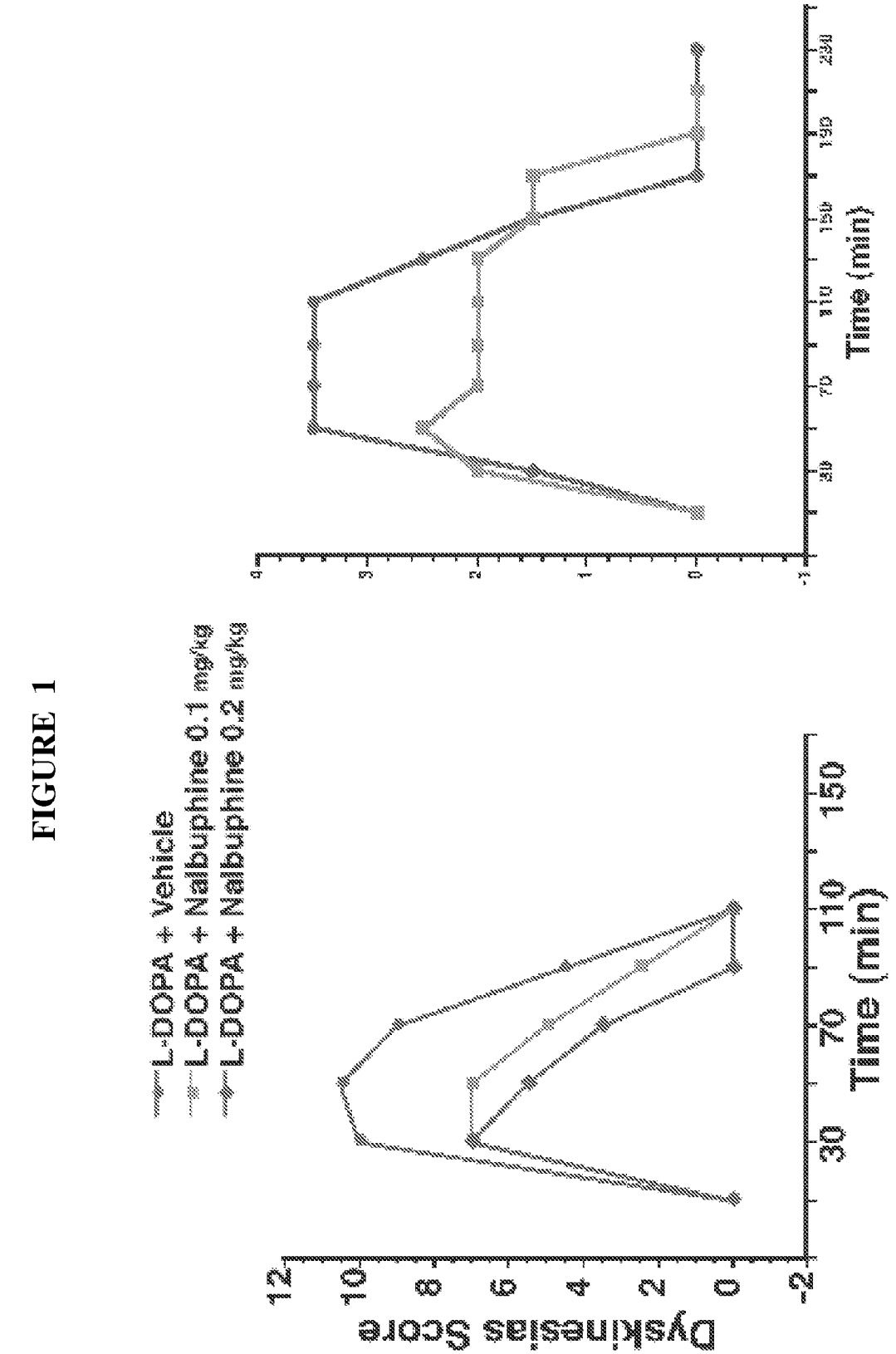
20. The use of any one of claims 1 to 4 wherein said Nalbuphine is for administration to a subject via a continuous infusion.

21. The use of claim 20, wherein said continuous infusion dose is at least 0.0001 mg/kg/day.

22. The use of any one of claims 1 to 5 wherein the Nalbuphine is for oral administration.

Date Reçue/Date Received 2020-07-27

FIGURE 1


L-DOPA + Vehicle
L-DOPA + Nalbuphine 0.1 mg/kg
L-DOPA + Nalbuphine 0.2 mg/kg
Dyskinesias Score
Time (min)
Time (min)

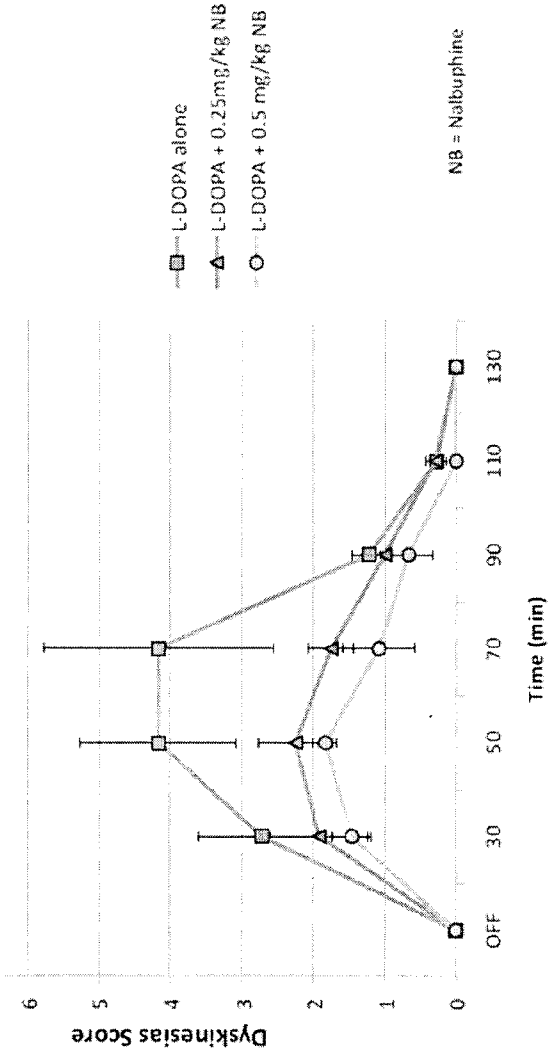

L-DOPA alone
L-DOPA + 0.25mg/kg NB
L-DOPA + 0.5 mg/kg NB
NB = Naltuphine
Dyskinesias Score
0
1
2
3
4
5
6
OFF
30
50
70
90
110
130
Time (min)

FIGURE 2