Title: USE OF OPIOID COMPOUND TO TREAT A NEUROLOGIC OR NEUROGENIC DISORDER

Abstract: The present invention relates to a novel use of opioid compounds for treatment of a neurologic or neurogenic disorder. Such neurologic or neurogenic disorders include lingual, pharyngeal, laryngeal, esophageal, urinary bladder sphincter, lumbar-lumbo-sacral spine, pelvis-pelvic limb paresis or paralysis. The invention provides a unique method of treating the specified disorder or disorder by administering to a subject in need of such a treatment a therapeutically effective amount of pharmaceutical formulation comprising an opioid compound.
USE OF AN OPIOID COMPOUND TO TREAT A NEUROLOGIC OR NEUROGENIC DISORDER

This application claims priority to U.S. Provisional Application 60/357,389, filed February 15, 2002.

TECHNICAL FIELD

This invention relates generally to methods and pharmaceutical compositions for treating neurologic and neurogenic disorders of the mammalian nervous system. Specifically, the invention relates to a novel use of opioid compounds for treatment of centrally and peripherally mediated neuropathies and neuromyopathies. The list of opioid treatable neuropathies and neuromyopathies includes but is not limited to lingual, pharyngeal, laryngeal, esophageal, urinary bladder sphincter, lumbar-lumbo-sacral spine, pelvis-pelvic limb paresis or paralysis.

BACKGROUND OF THE INVENTION

Overview Of The Mammalian Nervous System

The mammalian nervous system is comprised of the Central and Peripheral Nervous Systems. The Central Nervous System is comprised of the brain and its functional components. The Peripheral Nervous System is comprised of all the cranial and spinal nerves and their functional components. There are 12 pairs of cranial nerves and 36 to 37 pairs of spinal nerves, which provide the means of communication between the brain, spinal cord and the rest of the body.

Disorders involving the Central Nervous System, the Peripheral Nervous System or both systems together will impact the area of the body normally innervated by that system or systems. When the cause of a disorder of the nervous system originates from outside the nervous system, the disorder is termed Neurologic. When the cause of a disorder of the nervous system originates from within the nervous system, the disorder is termed Neurogenic.

Lingual paresis or paralysis is a disorder observed individually or as part of a larger neurologic or neurogenic syndrome. The etiologies of this disorder of the tongue may be inherited or acquired. Regardless of the cause, loss of partial or total lingual function will affect the ability of the individual to prehend food, pass the food
bolus to the back of the pharynx and interfere with the individual's ability to swallow food or water. Lingual paresis or paralysis results in the disorder known as "Oral or Lingual Dysphagia". If the individual's nutritional needs are not effectively addressed, death can occur as the result of the body's physical deterioration and eventual organ shutdown from the prolonged effects of dehydration, malnutrition and eventual starvation. To date there is no known cure for lingual paresis or paralysis. The focus of therapy remains on strategies to insure an adequate dietary intake of food and water and management of effective oral hygiene.

Pharyngeal paresis or paralysis is a disorder observed individually or as part of a larger neurologic or neurogenic syndrome. The etiologies of this disorder of the pharynx may be inherited or acquired. Regardless of the cause, loss of partial or total pharyngeal function can disrupt the normal gag and or swallow reflexes resulting in the ineffective swallowing of food and water, can lead to aspiration pneumonia as the opening into the trachea is ineffectively covered during swallowing, can allow regurgitation of food or fluid back up into the oral and nasal cavities, and can impair the normal passage of air into the trachea. Pharyngeal paresis or paralysis results in the disorder known as "Pharyngeal Dysphagia". If the individual's nutritional and airway needs are not adequately addressed, death can occur as the result of complications of starvation and or aspiration pneumonia. To date there is no known cure for pharyngeal paresis or paralysis. The focus of therapy remains on strategies to insure adequate nutritional intake while addressing continual problems associated with fluid and food aspiration into the lungs and their consequences.

Laryngeal paresis or paralysis is a disorder observed individually or as part of a larger neurologic or neurogenic syndrome. The etiologies of this disorder involving the larynx may be inherited or acquired. Regardless of the cause, loss of partial or total function of the larynx can impair one's ability to phonate, can cause an upper airway obstructive syndrome severely decreasing airflow into the lungs, and can allow aspiration of food and fluid into the trachea as the arytenoids fail to effectively close over its opening. If the medical affects of laryngeal paresis or paralysis are not effectively dealt with, death may occur as the result of complications from aspiration pneumonia, respiratory failure and finally cardiac arrest. To date there is no known cure for laryngeal paresis or paralysis. The focus of therapy remains on strategies to maintain an open and adequate airway into the trachea allowing sufficient oxygen to
reach the lungs and on strategies to deal with aspiration pneumonia and its consequences.

Esophageal paresis or paralysis is a disorder observed individually or as part of a larger neurologic or neurogenic syndrome. The etiologies of esophageal paresis or paralysis may be inherited or acquired. Regardless of the cause, loss of partial or total esophageal function can result in retention of masticated food and fluid in the esophagus, can lead to retention esophagitis, which can result in regurgitation of esophageal contents into the oral and nasal pharynx, and can allow aspiration of the regurgitated esophageal contents into the lungs. Esophageal paresis or paralysis results in a disorder known as "Megaesophagus". Death from "Megaesophagus" may ensue from the long-term effects of starvation, as a result of complications of "Retention Esophagitis", and or from the secondary complications of aspiration pneumonia. To date there is no known cure for esophageal paresis or paralysis. The focus of therapy remains on strategies to passively allow masticated food and fluid to flow from the oral pharynx to the stomach, and on medical strategies for treating the resultant esophagitis including neutralizing the affects of differing chemical compositions on mucosal surfaces when positional aids fail to prevent movement of foodstuffs passively back out into the oral/nasal pharynx.

Urinary bladder sphincter paresis or paralysis is a disorder identified individually, or as part of a larger neurologic or neurogenic syndrome. The etiologies of urinary bladder sphincter paresis or paralysis may be inherited or acquired. Regardless of the cause, loss of partial or total function of the urinary bladder sphincter can result in intermittent or continual leaking of urine out of the bladder. Urinary bladder sphincter paresis or paralysis results in a disorder known as "Neurogenic Urinary Bladder Sphincter Incontinence". Where the leaking urine flows or accumulates determines what symptoms are associated with the incontinence. Urethritis, Cystitis, Nephritis, Vaginitis, Perivulvar and Vulvar Vaginitis and Urine Scald Dermatitis are some of the secondary consequences associated with urinary bladder sphincter paresis or paralysis. To date there is no known cure for urinary bladder sphincter paresis or paralysis. The focus of therapy remains on strategies to control urine leakage as in Urinary Bladder Suspension Surgery, or strategies to absorb the leaking urine, treat primary and secondary areas of inflammation or infection, and keep the leaking and leaked on areas as clean, dry, and sanitary as possible.
Lumbar-lumbo-sacral spine paresis or paralysis is a disorder identified individually, or as part of a larger neurologic or neurogenic syndrome. The etiologies of lumbar-lumbo-sacral spine paresis or paralysis may be inherited or acquired. Regardless of the cause, this condition can cause progressive atrophy and weakness of the skeletal muscles over the lumbar and sacral spine. Lumbar-lumbo-sacral spine paresis or paralysis results in a disorder known as "Progressive Neuromuscular Atrophy of the Lumbar, Lumbo-Sacral Spine". As the disorder progresses, it becomes increasingly more difficult to use the back in even the most basic of functions such as in bending, straightening and turning the upper torso. To date there is no known cure for lumbar-lumbo-sacral spine paresis or paralysis. The focus of therapy remains on strategies to assist one with ambulation, sitting, standing and reclining such as specially designed walkers, canes, rales, ramps, power assisted lifts, assisted lifts, etc.

Pelvis-pelvic limb paresis or paralysis is a disorder identified individually, or as part of a larger neurologic or neurogenic syndrome. The etiologies of Pelvis-pelvic limb paresis or paralysis may be inherited or acquired. Regardless of the cause, this condition causes progressive atrophy, weakness and eventual paralysis of the muscles which make up the pelvis and pelvic limbs. Pelvis-pelvic limb paresis or paralysis results in a disorder known as "Progressive Neuromuscular Atrophy of the Pelvis and Pelvic Limbs". Progressive loss of muscle tone and strength in the pelvis and pelvic limbs make even rudimentary functions such as standing, sitting, rising, and ambulating almost impossible without some sort of external assistance. To date there is no known cure for pelvis-pelvic limb paresis or paralysis. The focus of therapy remains on strategies for assisted movements when standing, walking or sitting, such as specially designed walkers, canes, crutches and carts. Eventually any function requiring muscular movement or strength below the waist will fail.

In the preceding discussion each "disorder" and its clinical signs was described individually. It was also stated that each disorder could be identified as a part of a larger neurologic or neurogenic syndrome, where a syndrome is defined as two or more disorders and their clinical signs occurring together to form a recognized disease state. When the clinical signs associated with a disorder or a syndrome are the result of the dysfunction of a single nerve it is referred to as a "neuropathy". If the clinical signs associated with a disorder or a syndrome are the result of the dysfunction of two or more individual nerves, it is referred to as a "polyneuropathy". The dysfunctions
nerves in a neuropathy or polyneuropathy may be located in either the central nervous system (CNS), the peripheral nervous system (PNS), or in both nervous systems simultaneously.

These disorders or syndromes of neurologic or neurogenic origin which cause paresis or paralysis within the mammalian nervous system are often progressive in nature and can eventually result in permanent dysfunction of the particular organ or area of the body involved. As only palliative treatment is currently available for these debilitating conditions, there exists a considerable need for a cure and better therapeutic choices for each of the aforementioned disorders.

The present invention addresses this need by providing a novel use of a class of compounds, the Opioids, to effectively treat and ameliorate the symptoms associated with lingual, pharyngeal, laryngeal, esophageal, urinary bladder sphincter, lumbar-lumbo-sacral spine, pelvis-pelvic limb paresis or paralysis, whether identified alone or as part of a larger neurologic or neurogenic syndrome.

Identification of the specific nerve or group of nerves associated with a neurologic or neurogenic disorder or polyneuropathic syndrome, with their attendant clinical signs and symptoms, and documenting which opioid compound or compounds effectively treats and ameliorates the associated disease signs and symptoms, provides a unique opportunity to apply this knowledge to the treatment of other disease states caused by a neuropathic disorder or polyneuropathic syndrome that contain some or all of these same effectively treated clinical signs and symptoms as part of their signalment.

Examples of disease states which are seen individually or as part of a larger neurologic or neurogenic disorder, or syndrome, which have or should respond individually to treatment with a compound or compounds from the drug class Opioid, as when previously treated effectively as part of a larger neurologic or neurogenic Syndrome, include, but are not limited to, Cardiomyopathy, Centrally Mediated Depression, Congestive Heart Failure, and Paralytic Intestinal Ileus.

Examples of polyneuropathic syndromes which contain some, or all of the neurologic or neurogenic signs and symptoms which had been effectively treated previously, either alone as part of a disorder, or, as part of a larger neurologic or neurogenic syndrome, with a compound or compounds from the drug class Opioid, and should respond similarly to treatment with the same compound or compounds
include, but are not limited to, Multiple Autonomic Nervous System Dysfunction, Multiple Sclerosis, Muscular Dystrophy, Myasthenia Gravis and Parkinson's Disease.

**The Opioids, Mechanism Of Action**

Opioids are alkaloid compounds. The prototypic opioid, morphine, was first isolated from opium in the early nineteenth century. The opium alkaloids can be broadly divided into five distinct chemical classes: phenanthrene, benzylisoquinoline, tetrahydroisoquinoline, cryptopine, and miscellaneous (Remington's Pharmaceutical Sciences 433, 1975). Therapeutically useful drugs are primarily isolated from the phenanthrene and benzylisoquinoline classes. The principal phenanthrenes are morphine, codeine, and thebaine. The principal benzylisoquinolines are papaverine and noscapine.

The most common use of opioid compounds in today's prescription market is for their analgesic properties. The opioids produce their effects by binding to different types of opioid receptors throughout the central and peripheral nervous systems.

Opioids act within the central nervous system to elevate the pain threshold and to alter the psychological response to pain. The Opioids also act outside the brain, producing their pharmacologic effects by interacting with one or more of four (three major) opioid receptors (mu, sigma, kappa, and delta) located in the peripheral nervous system. The pharmacologic effects vary among the opioid derivatives, depending on the location in the body, and the type of interaction between the opioid and the receptor. It is currently understood that an opioid compound may bind simultaneously to one or more of the known opioid receptors (Mu, Delta, and Kappa), and that it is likely that several subtypes of receptors exist for each of the three major types of receptors.

Although the primary pharmacologic effects desired from most all opioids in use today, are analgesia, euphoria, and sedation without loss of consciousness (Reisine and Pasternak, 1966). The pharmacologic effects of opioids are now known to extend beyond the control of pain. One opioid formulation, Apomorphine, directly stimulates the chemoreceptor trigger zone in the brain, triggering an emetic or vomiting response, which is helpful in an emergency situation, where one wants to stimulate a vomiting response. Butorphanol, another opioid derivative, has been used as an antiemetic, to help control the vomiting induced by the chemotherapeutic agent Cisplatin (Schurig, et al., 1982). Additional gastrointestinal effects noted in response
to the administration of opioid compounds include, increase or decrease in the amount of hydrochloric acid secreted into the stomach, increase in tone in the antral portion of the stomach and upper duodenum, resting segmental tone is increased, markedly decreasing the propulsive movement of the intestinal contents, which is helpful in treating upper intestinal diarrhea, but can lead to the common problem of constipation if diarrhea is not present.

The present invention for the first time, establishes the therapeutic utility of the Opioid class of compounds not for the treatment of pain, but for the treatment of a number of specified neurologic or neurogenic disorders. Naturally occurring, endogenous opioid peptides (opiopeptins) have been shown to act as neurotransmitters and appear to act as modulators of neurotransmission or neurohormones. In addition, several opium derivatives found in nature (morphine, codeine and other related compounds (Reisine and Pasternak)), are also believed to act as modulators of neurotransmission or neurohormones, have also been found in mammalian cells. It is in this role as an endogenous opioid peptide, or a neurotransmitter replacement, that the opioids in this study are believed to exert their effect on the paretic or paralyzed muscle tissue, partially or completely reversing the effects of that paresis or paralysis on the target tissue.

In every disorder involved in this study, the area impacted by dysfunction of the nervous system, is the muscle tissue it innervates. When partial function remains in the innervated muscle tissue, it is termed paresis. When no function remains in the innervated muscle tissue, it is termed paralysis. When a pathologic disorder originates in the central or peripheral nervous system and results is partial or total loss of muscular function, it is termed a neuromyopathy.

This study establishes for the first time, the therapeutic use of Opioid compounds, not for the alleviation of pain, but to prevent, ameliorate, reduce or cure the symptoms associated with each of the following neuromyopathic disorders: Lingual Paresis/Paralysis, Pharyngeal Paresis/Paralysis, Laryngeal Paresis/Paralysis, Esophageal Paresis/Paralysis, Urinary Bladder Sphincter Paresis/Paralysis, Lumbar, Lumbo-Sacral Spine Paresis/Paralysis, and Pelvis, Pelvic Limb Paresis/Paralysis.

**SUMMARY OF THE INVENTION**

The present invention encompasses the novel use of an opioid compound to treat
one or more of the following neurologic or neurogenic disorders: lingual paresis or paralysis, pharyngeal paresis or paralysis, laryngeal paresis or paralysis, esophageal paresis or paralysis, urinary bladder sphincter paresis or paralysis, lumbar-lumbo-sacral spine paresis or paralysis, and pelvis-pelvic limb paresis or paralysis.

Another aspect of the present invention is the novel use of an opioid compound to treat disease states or symptoms identified previously as part of a disorder or syndrome, individually, as in, but not limited to, Cardiomyopathy, Centrally Mediated Depression, Congestive Heart Failure and Paralytic Intestinal Ileus. Such disorder or syndrome have been successful treated.

Another aspect of the present invention is the novel use of opioid compounds to treat one or more Polyneuropathic Syndromes with similar neurologic or neurogenic signs and symptoms, similarly, as in, but limited to, Multiple Autonomic Nervous System Dysfunction, Multiple Sclerosis, Muscular Dystrophy, Myasthenia Gravis and Parkinson's Disease.

The present invention further encompasses a method for treating a neurologic or neurogenic disorder comprising administering to a subject in need of such treatment a therapeutically effective amount of a pharmaceutical formulation comprising an opioid compound that prevents, treats, cures, ameliorates or reduces symptoms of said neurologic or neurogenic disorder. Preferably, the neurologic or neurogenic disorder is lingual, pharyngeal, laryngeal, esophageal, urinary bladder sphincter, lumbar-lumbo-sacral spine, or pelvis-pelvic limb paresis or paralysis.

In one aspect, the subject suffers from lingual paresis/paralysis. In another aspect, the subject suffers from pharyngeal paresis/paralysis. In another aspect, the subject suffers from laryngeal paresis/paralysis. In another aspect, the subject suffers from esophageal paresis/paralysis. In another aspect, the subject suffers from urinary bladder sphincter paresis/paralysis. In another aspect, the subject suffers from lumbar-lumbo-sacral spine paresis/paralysis. In another aspect, the subject suffers from pelvis-pelvic limb paresis/paralysis. In another aspect, the subject suffers from one, some or all of the specified disorders.

In a separate aspect, the compound contained in the pharmaceutical formulation is selected from the group of naturally occurring opium alkaloids including but not limited to Morphine, Codeine, Thebaine, Papaverine and Noscapine. In another aspect, the compound contained in the pharmaceutical formulation is selected from
the same group of naturally occurring opium alkaloids but in their immediate or extended release forms. Morphine Sulfate is an example of an immediate release, naturally occurring opium alkaloid. Morphine Sulfate Extended Release is an example of an extended release, naturally occurring opium alkaloid.

In a separate aspect, the compound contained in the pharmaceutical formulation is selected from the group of semi-synthetic opium alkaloids including but not limited to Heroin, Hydromorphone, Metapon, Oxymorphone, Levorphanol, Hydrocodone, Oxycodone, Tramadol, Nalorphine, Naloxone, and Naltrexone. In another aspect, the compound contained in the pharmaceutical formulation is selected from the same group of semi-synthetic opium alkaloids but in their immediate or extended release forms. Oxycodone Hydrochloride is an example of an immediate release, semisynthetic, opium alkaloid. Oxycodone Hydrochloride Sustained Release is an example of an extended release, semisynthetic, opium alkaloid.

In a separate aspect, the compound contained in the pharmaceutical formulation is selected from the group of synthetic opium alkaloids including but not limited to Meperidine and Congners, Methadone and Congeners, Levorphanol and Congeners, Phenazocine, Fentanyl, Propoxyphene and Ethoheptazine. In another aspect, the compound contained in the pharmaceutical formulation is selected from the same group of synthetic opium alkaloids but in their immediate or extended release forms. Fentanyl Citrate is an example of an immediate release, synthetic, opium alkaloid. The Fentanyl Patch is an example of a sustained release, trans-dermal, synthetic, opium alkaloid.

In summary, the pharmaceutical formulation contains either a naturally occurring, semi-synthetic or synthetic opioid compound in either its immediate or sustained release form, containing or not containing its salt and also containing a pharmaceutically acceptable carrier.

Administration of the pharmaceutical formulation is carried out within the context of a predetermined dosing regimen such that the agent is effective in the treatment of the specified neurologic/neuropenic disorder. The precise amount of the pharmaceutically effective medication administered will generally depend on the particular drug selected, the age and general condition, and, or, the pharmacological condition of the subject being treated, and the judgment of the prescribing physician. In general the subject is given a daily dose of the effective opioid in the range of
approximately 0.1mg to 200mg depending on the amount needed to sustain a therapeutic blood level, administered preferably, but not limited to, one to eight times in a twenty-four hour period. The drug delivery may be by, but not limited to, oral, intravenous, intramuscular, subcutaneous, transdermal or another acceptable route.

The present invention further encompasses the use of an opioid compound having an amount effective to prevent, ameliorate, reduce or cure paresis or paralysis in the manufacturer of a medicament for use in a method of treating a neurologic or neurogenic disorder or syndrome in a subject in need of such treatment, wherein said medicament is administered in an amount sufficient to prevent, ameliorate, reduce or cure the symptoms of said neurologic or neurogenic disorder or syndrome in said subject.

The present invention further encompasses a method for testing or identifying an opioid compound or a pharmaceutical formulation capable of preventing, ameliorating, reducing or curing a neurologic or neurogenic disorder or syndrome, comprising: (a) determining the function of an organ of a subject, wherein said subject suffers from a neurologic or neurogenic disorder or syndrome, (b) administering said opioid compound or said pharmaceutical formulation to said subject, (c) determining the function of said organ of said subject, and (d) identifying said opioid compound or said pharmaceutical formulation wherein said function determined in step (c) is prevented, ameliorated, reduced or cured compared to said function determined in step (a). In one embodiment, when necessary the method involves repeating steps (a)-(d) for testing or identifying more one opioid compound or pharmaceutical formulation. When necessary the method can further involve repeating steps (b) and (c) one or more times for each opioid compound or pharmaceutical formulation tested. Preferably, the function of an organ is neuologic or neurogenic lingual, pharyngeal, laryngeal, esophageal, urinary bladder sphincter, lumbar-lumbo-sacral spine, or pelvis-pelvic limb control or function. Preferably, the step of determining the function of an organ is grading the function using a grading system. The opioid compound tested is either a known or unknown opioid compound.

DETAILED DESCRIPTION OF THE INVENTION

Mode(s) For Carrying Out The Invention

Throughout this disclosure, various publications, patents and published patent
specifications are referenced by an identifying citation. The disclosures of these publications, patents and published patent specifications are hereby incorporated by reference into the present disclosure.

5 Definitions

As used in the specifications and claims, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "an opioid compound" includes a plurality of opioids, including mixtures thereof.

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular drugs or drug delivery systems, and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

The terms "treat", "treating" and "treatment" as used herein, refer to effecting a reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms or their underlying cause, and/or amelioration of damage caused by the disorder. The present method of "treating" a neurologic/neurogenic disorder, as the term is used herein, thus encompasses both prevention of the disorder in a predisposed individual and treatment of the disorder in a clinically symptomatic individual.

The terms "active agent," "drug" and "pharmacologically active agent" are used interchangeably herein to refer to a chemical material or compound that induces a desired effect. In the preferred embodiment herein, the terms refer to an opioid compound which is being administered into a subject prone to or exhibiting the claimed symptoms, preferably by, but not limited to, oral, subcutaneous, intramuscular, intravenous, transdermal, or another acceptable route. Included are derivatives and analogs of those compounds or classes of compounds specifically mentioned herein or known in the art, which also induce the desired effect.

As used herein, the term "opioids" refers to substances, natural, semisynthetic, or synthetic, which bind to a centrally and/or peripherally located opioid receptor to produce an agonist action, a partial agonist action (agonist/antagonist) or an antagonistic action.

"Carriers" or "vehicles" as used herein refer to carrier materials suitable for drug
administration. Carriers and vehicles useful herein include, but are not limited to any such material known in the art, which is nontoxic and does not interact with other components of the composition in a deleterious manner.

By a "therapeutically effective" amount of a drug or "pharmacologically active" agent or "pharmaceutical formulation" is meant a nontoxic but sufficient amount of the drug, agent or formulation to provide the desired effect, i.e., treatment of a neurologic/neurogenic disorder that causes a paresis or paralysis. Such paresis or paralysis include, but are not limited to: lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, esophageal paresis/paralysis, urinary bladder sphincter paresis/paralysis, pelvis-pelvic limb paresis/paralysis, and combination thereof. Treatment includes preventing, ameliorating, reducing or curing a disease state, disorder or syndrome.

"Immediate-release" is defined for purposes of the present invention as the release of the drug (e.g., opioid compound) at such a rate that therapeutic blood (e.g., plasma) levels required by the body are reached, and maintained for a period 6 hours or less.

"Extended or sustained-release" is defined for purposes of the present invention as the release of the drug (e.g., opioid compound) at such a rate that therapeutic blood (e.g. plasma) levels required by the body are reached and maintained for a period lasting over 6 hours and preferably lasting 12-36 hours or longer.

A "subject," "individual" or "patient" is used interchangeably herein, which refers to a vertebrate, preferably a mammal. The mammal is either a human or a non-human. Non-human mammals include but are not limited to, mice (murines), rats, simians, humans, farm animals, sport animals, and pets such as dogs and cats.

25 **Active Agents For The Treatment Of The Neuologic or Neurogenic Discorders**

In order to carry out the method of the invention, an opioid compound is administered to an individual prone to or exhibiting one or more of the claimed disease state or symptoms of paresis or paralysis, wherein such paresis or paralysis affects a voluntary or involuntary muscle, or a group thereof. The muscles include those innervated by one or more of the cranial nerves (1-12) or the nerves from or of the CNS. Such paresis or paralysis include lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, esophageal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar-lumbo-sacral spine paresis/paralysis, and
pelvis-pelvic limb paresis/paralysis. Preferably, the symptom is a disease state of the muscle. More preferably, the disease state is the atrophy or wasting of the muscle.

The use of the opioid compound results in preventing, ameliorating, reducing or curing the paresis or paralysis. The opioid compound is also administered for the specific purpose of preventing, ameliorating, reducing or curing the paresis or paralysis. One of the results is the cessation and/or reversal of the atrophy or wasting of the muscle.

In one embodiment, the opioid compound is any compound that is capable of binding to the mu, sigma, kappa or delta opioid receptor, or ORL1 receptor. In another embodiment, the opioid compound is any compound that is capable of binding to either (1) only one of the above described receptors or (2) all the above described receptor except one of the above described receptors.

In one embodiment, the opioid compound is a naturally occurring opium alkaloid. Preferably, the naturally occurring opium alkaloid is morphine, codeine, thebaine, papaverine, or noscapine. In another embodiment, the opioid compound is a semi-synthetic opium alkaloid. Preferably, the semi-synthetic opium alkaloid is heroin, hydromorphone, metapont, oxymorphone, levorphanol, hydrocodone, oxycodone, tramadol, nalorphine, naloxone, or naltrexone. In another embodiment, the opioid compound is a synthetic opium alkaloid. Preferably, the synthetic opium alkaloid is meperidine and congener, methadone and congeners, levorphanol and congeners, phenazocine, fentanyl, propoxyphene and ethoheptazine. Preferably, the opioid compound is a natural, semi-synthetic or synthetic formulation in its' immediate or sustained release form.

The opioid compound can be a phenathrene, phenylheptylamine, or phenylpiperidine. Examples of phenathrenes include, but are not limited to, morphine (MS Contin), heroin, hydromorphone (Dilaudid), oxymorphone (Numorphan), codeine (Tylenol 3, 4), hydrocodone (Vlcodin, Lorcel), oxycodone (Percocet, OxyContin®, Tylo), and etorpine (Immobilon). Examples of phenylheptylamines include, but are not limited to, methadone, methadyl acetate, dimeheptanol (methadol), isomethadone, dipipanone, dimenoxidol, and propoxyphene (Dravon). Examples of phenylpiperidines include, but are not limited to, meperidine (Demerol), properidine, alphaprodine, beta-promedol, alfentanyl (Alfenta), fentanyl (Sublimaze), carfentanyl, lofentanil, and sufentanil (Sufenta).
Examples of opioid compounds which can be used in the present invention include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, beta-hydroxy 3-methylfentanyl, bezitramide, buprenorphine, butorphanol, carfentanil, clonitazene, codeine, cyclozocine, desomorphine, dextromoramide, dezocine, diacetyl morphine (heroin), diampromide, dihydrocodeine, dihydroetorphine, dihydromorphine, dimenoxadol, dimeheptanol, dimethylthiambutene, dioxaphetylbutyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, fentanyl, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, LAAM, levalorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, O-methylnaltrexone, metopon, morphine, myophene, nalbuphine, nalorphine, naloxone, naltrexone, narceine, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorph, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, remifentanil, sufentanil, tildine, tramadol, salts thereof, mixtures of any of the foregoing, mu-agonists, mixed mu-agonists/antagonists, mu-antagonists, combinations of the preceding and the like in their natural, semi-synthetic or synthetic states and in their immediate or sustained release formulations.

Commercially available oxycodone formulation include: OxyContin®, Supeudol®, Roxycodeone®, Endocet®, Oxyct®, Percocet®, Roxicet®, Roxilox®, Tylox®, Roxicet®, Percodan®, Roxiprin®, Oxycodan®.

The opioid compound can be any pharmaceutically acceptable salt thereof or any of the compounds disclosed above.

Thebaine and derivatives and analogues thereof can be synthesized by the methods disclosed by U.S. Patent Nos. 6,136,817 and 6,365,742. 14-hydroxydihydromorphinones, including oxymorphone, naloxone, naltrexone, oxymorphone, naloxazone, naltrexazone, oxymorphone, naloxonazone, and naltrexazonine, and analogues thereof can be synthesized by the methods disclosed by U.S. Patent No. 4,803,208. Morphine derivatives and analogues thereof can be synthesized by the methods disclosed by U.S. Patent Nos. 6,150,524 and 6,476,044. Opioids and opioid antagonists include the compounds disclosed by U.S. Patent Nos. 4,816,586 and 5,352,680, and U.S. Patent Application Publication No. US
Two different opioid compounds can be combined: a first component and a second component. In one embodiment, the first component is an opioid agonist and the second component is an opioid antagonist. Preferably, the second component blocks at least a portion of the action of the first component. This blocking results is a reduction of adverse side-effects, such as one or more of addiction, constipation, sedation. In a preferable combination, the first component is morphine, tramadol or hydrocodone, and the second component is naltrexone. In one embodiment, the first and second components can be administered as a pre-mixed combination. In another embodiment, the first and second components can be administered separately.

An opioid antagonist can be a partial agonist-antagonist or a narcotic antagonist. Examples of partial agonist-antagonists include, but are not limited to, noscapine, pentazocine (Talwin), butorphanol (Stadol), and nalbuphine (Nubain). Examples of pure narcotic antagonists include, but are not limited to, naloxone, nalorphine (Nalline), naltrexone (ReVia), nalmefene and nadine (Enzapride).

**Pharmaceutical Formulations And Modes Of Administration**

The active agent prepared in a pharmaceutical formulation is administered to treat lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, esophageal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar-lumbo-sacral spine paresis/paralysis, and pelvis-pelvic limb paresis/paralysis.

The pharmaceutical compositions can be administered by any suitable route including but not limited to oral, rectal, nasal, topical (including but not limited to transdermal, aerosol, buccal, and sub-lingual), parenteral (including but not limited to subcutaneous, intramuscular, intravenous, intraperitoneal, intrathecal, and intracranial), or by Inhalation (including but not limited to nebulization, or by propellant atomizer or propellant inhaler).

The preferred route of administration will depend on the many variables i.e. (age, condition of the patient, concurrent diseases, formulations available for delivery).

Depending on the specific mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid, or liquid. Examples include but are not limited to tablets, suppositories, powders, liquids, suspensions, creams, ointments, lotions or the like, preferably in unit dosage form for single administration of a
precise dosage. The pharmaceutical composition comprises a therapeutically effective amount of the opioid compound. The pharmaceutical composition can further comprise a pharmaceutically or veterinarily acceptable carrier. The pharmaceutical composition can also further comprise other pharmaceutical agents, adjuvants, diluents, buffers, etc. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

For solid compositions, conventional nontoxic solid carriers include, for example, but are not limited to pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., an active compound as described herein and optional pharmaceutical adjuvant in an excipient, such as, but not limited to for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as, but not limited to wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington: The Science and Practice of Pharmacy, Nineteenth Ed. (Easton, Pa.: Mack Publishing Company, 1995).

Formulations of the present invention suitable for oral administration may be presented as discrete units such as, but not limited to capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as, but not limited to a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as, but not limited to a powder or granules, optionally mixed with but not limited to a binder (e.g., povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g., sodium starch glycolate, cross-linked povidone, cross-
linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded
tables may be made by molding in a suitable machine a mixture of the powdered
compound moistened with an inert liquid diluent. The tablets may optionally be
coated or scored and may be formulated so as to provide slow or controlled release of
the active ingredient therein using, for example, hydroxypropylmethyl cellulose in
varying proportions to provide the desired release profile. Tablets may optionally be
provided with an enteric coating, to provide release in parts of the gut other than the
stomach.

The opioid useful herein may be delivered through the skin using conventional
transdermal drug delivery systems, i.e., transdermal “patches” wherein the agent is
typically contained within a laminated structure that serves as a drug delivery device
to be affixed to the skin. In such a structure, the drug composition is typically
contained in a layer, or “reservoir,” underlying an upper backing layer. The laminated
device may contain a single reservoir, or it may contain multiple reservoirs. In one
embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically
acceptable contact adhesive material that serves to affix the system to the skin during
drug delivery. Examples of suitable skin contact adhesive materials include, but are
not limited to, polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates,
polyurethanes, and the like. Alternatively, the drug-containing reservoir and skin
contact adhesive are present as separate and distinct layers, with the adhesive
underlying the reservoir which, in this case, may be either a polymeric matrix as
described above, or it may be a liquid or hydrogel reservoir, or it may take some other
form.

Pharmaceutical compositions for topical administration according to the present
invention may also be formulated as, but not limited to for example, an ointment,
cream, suspension, lotion, powder, solution, paste, gel, spray, aerosol or oil.

Formulations for rectal administration may be presented as a suppository with a
suitable base comprising, for example, cocoa butter, or a salicylate.

Formulations suitable for nasal administration, wherein the carrier is a solid,
include a coarse powder having a particle size, for example, in the range of about 20
to about 500 microns which is administered in the manner in which snuff is taken, i.e.,
by rapid inhalation through the nasal passage from a container of the powder held
close up to the nose. Suitable formulations wherein the carrier is a liquid for

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administration as, for example, nasal spray, nasal drops, or by aerosol administration
by nebulizer, include aqueous or oily solutions of the agent.

Formulations suitable for parenteral administration include aqueous and non-
aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers,
bacteriostats and solutes which render the formulation isotonic with the blood of the
intended recipient; and aqueous and non-aqueous sterile suspensions which may
include suspending agents and thickening agents, and liposome’s or other
microparticulate systems which are designed to target the compound to blood
components or one or more organs. The formulations may be presented in unit-dose
or multi-dose sealed containers, for example, ampules and vials, and may be stored in
a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid
carrier, for example, water for injections, immediately prior to use. Extemporaneous
injection solutions and suspensions may be prepared from sterile powders, granules
tablets of the kind previously described.

In one embodiment, the pharmaceutical formulation has the opioid compound
prepared as an immediate or sustained-release form. A variety of sustained-release
forms of opioids are known in the art (e.g., U.S. Patent Nos. 5,958,459; 6,103,261;
6,294,195; 6,162,467). To prepare the sustained-release forms, the selected opioids
are typically incorporated into, but not limited to, a sustained release matrix;
incorporated into a sustained-release coating; incorporated as a separated sustained-
release layer with an immediate release layer; or are incorporated as a powder,
granulation, etc., in a gelatin capsule.

The coating formulations are typically capable of producing a strong, continuous
film that is smooth and elegant, capable of supporting other pigments and other
coating additives, non-toxic, inert, and tack-free. A variety of hydrophobic
substances are suitable for preparing the coating. Non-limiting exemplary materials
include hydrophobic polymers such as acrylic polymer, methylcellulose, or a mixture
thereof.

Preferred sustained-release matrix comprises a polymer including but not limited
to pharmaceutically acceptable gum, an alkylcellulose, a cellulose ether, an acrylic
resin, protein-derived materials, and mixtures of the forgoing.

It should be understood that in addition to the ingredients particularly mentioned
above, the formulations of this invention can further comprise other agents
conventional in the art having regard to the type of formulation in question; for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents. It also is intended that the agents, compositions and methods of this invention be combined with other suitable compositions and therapies.

**Dosage**

The amount of active agent administered and the dosing regimen used, is dependent on the particular drug selected, the age and general condition, or the pharmacological condition of the subject being treated, the severity of the subjects condition, and the judgment of the prescribing physician. Preferably, the daily drug dosage will be administered one to eight times, preferably one to four times daily or in a 48-hour period. Preferably, a daily dose of an active agent when administered ranges from 0.1mg to 200mg, depending on the half-life of the drug in the treated subject, the availability of the active compound via the chosen route of administration, and the ability of the drug to sustain a therapeutic level in the patient. The dosing regimen can be modulated in order to achieve the desired effect. More preferably, the daily dose ranges from 0.1mg to 100mg. Even more preferably, the daily dose ranges from 0.1mg to 80mg. Even much more preferably, the daily dose ranges from 1mg to 80mg. Even further much more preferably, the daily dose ranges from 3mg to 40mg.

Preferably, when a subject is in the range of 60 to 80 pounds, a starting dose of OxyContin®, is 5-10mg given every 12 hours. If a subject starts to show the symptoms of drug tolerance, the dose is elevated by 5 mg every 12 hours. The dose of medication is adjusted according to the weight and need of an animal, to ameliorate the presenting symptoms.

Preferably, when a subject is in the range of 60 to 80 pounds, a starting dose of Morphine Sulfate Extended Release, is 7½ to 15 mg given every 12 hours. If a subject starts to show the symptoms of drug tolerance, the dose is elevated by 7 ½ mg every 12 hours.

The lowest dosage is the least amount of the pharmaceutical formulation sufficient to prevent, ameliorate, reduce or cure the symptom of a neurologic or neurogenic disorder or syndrome. Preferably, the lowest dose of an opioid formulation used is this study, to control the presenting symptoms, was, Oxycodone immediate release, in
suspension, 3mg administered every 12 hours, to a 47 lb subject.

The highest dosage is the maximum amount of the pharmaceutical formulation that can prevent, ameliorate, reduce or cure the symptom of a neurologic or neurogenic disorder or syndrome without producing sufficient adverse side effect(s) in the subject that is not justified relative to benefit of the preventing, ameliorating, reducing or curing of the symptom of a neurologic or neurogenic disorder or syndrome. Preferably, the highest dose of an opioid formulation used in this study was OxyContin®, 40mg. More preferably, this is administered at 2 (40mg) tabs given every a.m., and 1 (40mg) tab given every p.m. Preferred unit dosage formulations are those containing a daily dose or unit, daily sub dose, as herein above recited, or an appropriate fraction thereof, of an agent.

The dose of medication is adjusted according to the weight and need of an animal, to ameliorate the presenting symptoms. One of ordinary skill in the art through routine experimentation has the means to determine the adjustment needed.

Means Of Evaluating The Effectiveness The Effectiveness Of A Dose Of An Opioid Formulation Administered To A Subject Suffering With A Neurologic Or Neurogenic Disorder

In order to evaluate the effectiveness of a dose of an Opioid formulation, over time, when being used to treat the symptoms of a neurologic/neurogenic disorder or syndrome, the following grading protocol is a means to quantify and document the neurologic/neurogenic function of the target organ or organs affected by the neuropathy or polyneuropathy at the start and conclusion of the time interval.

In this regard, an organ that functions normally is considered to be neurologically normal when there is no neuropathology affecting its function. Any partial loss of function in that organ that is neurologic/neurogenic in origin is termed Paresis. Total loss of function in that organ that is neurologic/neurogenic in origin is termed Paralysis. Because in most cases an organ can be clearly identified as having normal neurologic function, decreased neurologic function (paresis), or no neurologic function (paralysis), the documenting of the degree of remaining neurologic function of an organ lends itself to a simple grading system. An organ that functions normally and is considered to be neurologically normal receives the highest grade of (4). An organ that has no function as a result of a neurologic/neurogenic disorder or syndrome
and is paralyzed, receives the lowest grade of (0). An organ that has lost partial
function (Paresis) as a result of a neurologic/neurogenic disorder or syndrome
receives a grade of (2) or (3) depending on the degree of neurologic function
remaining.

An increase of the grading of a function in a subject, after administration of an
opioid compound or pharmaceutical formulation, indicates that the pharmaceutical
formulation is effective in preventing, ameliorating, reducing or curing a symptom of
the neurologic or neurogenic disorder affecting the function. The higher the grade of
neurologic or neurogenic function received while on a medication, the more effective
that pharmaceutical formulation of medication is in preventing, ameliorating,
reducing or curing the symptoms of the neurologic or neurogenic disorder affecting
that function.

Application of this grading system to the individual disorders described previously
would proceed as follows:

Lingual (Paresis/Paralysis): Grade (4), observation of normal lingual musculature,
normal lingual movement while swallowing and normal lingual withdrawal in
response to pinching with a hemostat. Grade (0), Atrophy of Lingual musculature,
inability to swallow a bolus of food, audible choking and gagging and no Lingual
withdrawal in response to pinching with a hemostat. Grade (2) or (3) depending on
the degree of lingual musculature remaining, the amount Lingual movement during
attempted swallowing and degree of withdrawal remaining in response to pinching
with a hemostat.

Pharyngeal (Paresis/Paralysis): Grade (4), normal swallowing of a bolus of food
or liquid. No audible obstructive airway sounds. No choking, or gagging sounds
audible. Grade (0) No ability to swallow a bolus of food of liquid, audible obstructive
airway sounds with choking and gagging audible. Grade (2) or (3) depending on the
degree of swallow reflex remaining the amount of audible obstructive airway sounds
present and the degree of choking and gagging present.

Laryngeal (Paresis/Paralysis): Grade (4), Normal unobstructed flow of air into and
out of the Larynx with normal vocalization. Grade (0), Obstructed flow of air into the
larynx with obstructed upper airway sounds, choking and gagging noted, and loss of
vocalization. Grade (2) or (3), depending on the amount of unobstructed airflow
remaining, the amount of choking and gagging noted and the degree of vocalization
remaining. An exemplar of a grading system for laryngeal function, that is further divided into breathing, swallowing, laryngospasm, jaw tone, and overall exposure of the larynx for examination, is described in Gross, et al. (J. Am. Animal Hosp. Assoc. 38:503-6. 2002).

Esophageal (Paresis/Paralysis): Grade (4), Normal passage of a bolus of food or fluid, after swallowing, from the back of the throat into the stomach. Grade (0), delayed or impaired passage of a bolus of food or fluid, after swallowing, from the back of the throat into the stomach, due to a lack of peristaltic contractions within the esophagus, with possible secondary symptoms of regurgitation, esophageal pain and halitosis. Grade (2) or (3), depending on the degree of peristaltic muscular contraction remaining in the esophagus and the extent of the impairment to the passage of a bolus of food or fluid from the back of the throat, after swallowing, into the stomach, and the secondary symptoms associated with the impairment.

Urinary Bladder Sphincter (Paresis/Paralysis): Grade (4), Normal Urinary Bladder Sphincter Function, normal ability to store and pass urine. Grade (0), no Urinary Bladder Sphincter function with continual leaking of urine out of the bladder and subsequently out of the urethra, with secondary consequences including urine scald, moist dermatitis, urethritis, cystitis, nephritis. Grade (2) or (3), depending on the degree of Urinary Bladder Sphincter function remaining and the amount of urine leaking with its secondary side effects.

Lumbar, Lumbo-Sacral (Paresis/Paralysis): Grade (4), Normal amount and function of muscles that are responsible for moving the Lumbar, Lumbo-Sacral Spine while bending, moving the back, and supporting the lower torso. Grade (0), Atrophy and loss of all tone of the muscles that are responsible for movement of the Lumbar, Lumbo-Sacral Spine rendering the body incapable of supporting the back and lower torso and thus preventing any voluntary movement of this part of the body. Grade (2) or (3), depending on the amount of muscle and muscle tone remaining and the extent to which voluntary support and movement of the lower back and torso remain.

Pelvis, Pelvic Limb (Paresis/Paralysis): Grade (4), Normal amount and function of muscles that are responsible for extending and flexing the joints of the Pelvic Limbs. Grade (0), Atrophy and loss of all tone of the muscles that are responsible for extending and flexing the joints of the Pelvic Limbs, rendering the Pelvic Limbs incapable of supporting the body and unable to ambulate. Grade (2) or (3), depending
on the amount of muscle and muscle tone remaining and the extent to which voluntary support and movement of the Pelvic limbs is possible.

The present invention also encompasses the use of an opioid compound having an amount effective to reduce paresis or paralysis in the manufacturer of a medicament for use in a method of treating a neurologic or neurogenic disorder in a subject in need of such treatment, wherein said medicament is administered in an amount sufficient to prevent, ameliorate or reduce the symptoms of said neurologic or neurogenic disorder in said subject. The medicament is effective or efficacious in the treatment of any of the neurologic or neurogenic disorder disclosed above. The medicament can further comprise a mixture of two or more opioid compounds. The medicament can be of an immediate or sustained release form. Preferably the medicament is administered solely or only for treating a neurologic or neurogenic disorder, i.e., it is administered to a subject that is not in need of pain relief, anesthesia, emesis or an anticholinergic effect. Pain relief includes relief of moderate to severe pain in an acute or chronic setting.

Illustrations of the use of opioid formulations for the treatment of specified neurologic/neurogenic disorders are provided in the example section below. The examples are provided as a guide to a practitioner of ordinary skill in the art, and are not meant to be limiting in any way.

EXAMPLES

Example 1

The following case study establishes the efficacy of a formulation of a semi-synthetic, sustained release, opioid agonist, Oxycodone hydrochloride, (OxyContin®) in particular, in the treatment of pharyngeal paresis/paralysis, laryngeal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar and lumbo-sacral spine paresis/paralysis, and pelvis and pelvic limb paresis/paralysis. Further description and means of usage of OxyContin® is found in the package insert of OxyContin® (Purdue Pharma LP, Stamford, CT).

"SR", an 8 1/2 year old spayed, female, Rhodesian Ridgeback (dog), suffers from a neurologic/neurogenic syndrome consisting of the following disorders: pharyngeal paresis/paralysis, laryngeal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar and lumbo-sacral spine paresis/paralysis, and pelvis and
pelvic limb paresis/paralysis.

Historically the owner reports a progressive exercise intolerance attributed to an increasing difficulty breathing and a progressive weakness and incoordination of the rear legs resulting from the loss of muscle mass over the lumbar and lumbo-sacral spine, pelvis and pelvic limbs. Excessive panting, choking and gagging are noted throughout the day even if the temperature is cool and the body is at rest. Leaking of urine is noted as a continual problem and a stagnant urine odor is detectable from the area of the vulva.

On physical examination the mouth is open, and panting with increased airway resistance is audibly noted. The tongue is visibly drier then usual. There is visible muscle atrophy over the lumbar and lumbo/sacral spine, pelvis and pelvic limbs, as evidenced by visible and palpable bony prominences in each of these affected areas. There is a stagnant urine smell coming from the area of the vulva.

The mouth was opened and the tongue pulled out to allow visualization of the throat. A small but ineffective swallow reflex is noted. The ineffective swallow reflex allows a small pool of sticky saliva to collect at the opening of the arytenoids, which additionally have lost their paradoxical outward movement during inspiration. The inspiration of pooled, sticky saliva into the tracheal opening causes a continual cough response, which in turn causes chronic inflammation of the arytenoids.

Chronic inflammation of the arytenoids causes swelling of the mucosal tissues, increasing resistance to air movement through the swollen, therefore smaller arytenoid opening. More effort is therefore used to inspire.

The initial medication selected to treat the symptoms of this polyneuropathy was the semi-synthetic, sustained release opioid agonist, oxycodone hydrochloride (OxyContin®), 20mg/tablet, dosed at 1/2 tablet every 12 hours.

After 1 week of administration there were no further symptoms of pharyngeal or laryngeal paresis/paralysis reported by the owner. Panting was no longer observed at inappropriate times and the sounds of restrictive air movement were no longer audible. Additionally, it was reported that the leaking of urine had now completely stopped.

After 2 weeks of administration the patient's body movement during ambulation, showed an almost complete return to normal. The previously described symptoms of weakness and incoordination were gone. The previously visible bony prominences of
the vertebrae, pelvis and pelvic limbs were now almost completely covered with visible and palpable muscle tissue. Further, the owner reported that the urinary tract incontinence had stopped.

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Example 2

The following case study establishes the efficacy of a formulation of a semi-synthetic, immediate release, opioid agonist, Oxycodone hydrochloride (Roxicodone®), for the treatment of lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, esophageal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar-lumbo-sacral spine paresis/paralysis, and pelvis-pelvic limbs paresis/paralysis. This case also establishes the fact that an immediate release but not a sustained release formulation of Oxycodone hydrochloride is required to maintain a therapeutic level of medication to effectively treat and resolve this dog's polyneuropathy.

"J.S.", an 11 year old spayed, female, Standard Poodle (dog), presents with a neurologic/neurogenic syndrome consisting of the following disorders; lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, esophageal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar-lumbo-sacral spine paresis/paralysis, and pelvis-pelvic limbs paresis/paralysis.

Historically, "J.S.'s symptoms include, general body weakness, difficulty swallowing, difficult, noisy breathing, reflux of gastric acid into her esophagus, regurgitation of gastric acid from the esophagus into her oral and nasal cavities, with accompanying oral and nasal discharges. Visible wasting of the muscles over her lumbar and lumbo-sacral spine, and pelvis and pelvic limbs made it difficult to rise from a sitting position or walk without stumbling. She also exhibited an uncontrolled leaking of urine.

Her condition was so unstable at presentation that it took 72 hours to sort out and address all her secondary medical problems. At this point only the underlying, polyneuropathic syndrome remained whose symptoms included: lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, esophageal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar-lumbo-sacral spine paresis/paralysis, and pelvis-pelvic limbs paresis/paralysis.

The initial medication selected to treat her polyneuropathy was the sustained-
release, semi-synthetic opioid agonist, Oxycodone Hydrochloride (OxyContin®). Within 2-3 hours of administering the initial dose (1/8 of a 10mg tablet every 12 hours), many of the neuropathic symptoms began to subside.

Initially, she appeared more alert and interested in her surroundings. Shortly thereafter, the volume and strength of her respiration began to improve. As it did, most if not all of the obstructed laryngeal sounds seemed to subside. When asked to go outside for a walk, this dog who previously was too weak to stand, stood up, shook herself as if shaking water from her coat, and walked briskly towards the front clinic door. When outside, she squatted, supporting her weight easily, urinated, stood back up and trotted back to the clinic door. She was sent home with the same medication, dose and dosing interval and instructed to call daily with progress reports.

Her recovery had progressed so rapidly the night before, that it was shocking to hear from the owners the following day, that her condition had deteriorated almost as quickly, overnight. On examination she was in fact very tired and reluctant to move or obey even simple commands such as heel or stand. Her head was hanging and her newly found interest in life had all but receded. Her heart rate, which had been between 120-140 bpm only yesterday, was now only 60-80 bpm at rest. Her respiratory rate, which had been markedly elevated, the prior day, was now very depressed.

These findings were disheartening, but one glaringly obvious difference did stand out. Although her body, heart and respiratory rates remained depressed, she was still breathing, without any of the obstructive sounds symptomatic of her presenting pharyngeal or laryngeal paresis/paralysis.

On an educated hunch the medication was discontinued and the owners kept her stable and reported her vital signs daily. After 48 hours her cardiac and respiratory rates began to rise and other symptoms of what turned out to be a drug induced depression began to resolve. What had been observed were in fact symptoms of an opioid overdose.

After several therapeutic trials it was finally established that the correct type of opioid necessary to control the symptoms of her polyneuropathic syndrome was a semi-synthetic, immediate, not sustained release formulation of Oxycodone Hydrochloride (Roxycode®). The correct dose and frequency of medication was established at (2 drops of Roxycode in syrup, 20mg/ml, every 12 hours). With this
formulation she no longer suffers from the symptoms of General Body Weakness, Lingual, Pharyngeal, Laryngeal, Esophageal, Bladder Sphincter, Lumbar, Lumbo-Sacral, Pelvis and Pelvic Limb Paresis/Paralysis.

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Example 3

The following case study establishes the effectiveness of a formulation of a semi-synthetic, sustained release, opioid agonist, Oxycodone hydrochloride (OxyContin®) for the treatment of a polyneuropathic syndrome, and the return of the ameliorated symptoms when a naturally occurring, sustained release, opioid agonist, Morphine Sulfate, with an equivalent amount of opioid, was substituted in its place. The disorders in the syndrome include lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar-lumbo-sacral spine paresis/paralysis, and pelvis-pelvic limb paresis/paralysis.

10 After the establishment and maintenance of an effective therapeutic level of a semi-synthetic, sustained release, opioid agonist (OxyContin®), which ameliorated the documented polyneuropathic syndrome, a change to another formulation in the class of opioids, a naturally occurring, sustained release, opioid agonist, Morphine Sulfate, with an equivalent amount of opioid, was not effective in maintaining a therapeutic blood level necessary to treat the existing polyneuropathy. All the presenting signs of this dog returned within one week of the medication change.

"ML", a 13 1/2 year old, spayed, female, large breed canine cross (dog), suffers with a neurologic/neurogenic syndrome consisting of the following disorders: lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar-lumbo-sacral spine paresis/paralysis, and pelvis-pelvic limb paresis/paralysis.

Historically her symptoms include, continual panting, dryness of the tongue and mouth, difficulty swallowing, choking, gagging and coughing, inspiratory difficulty accompanied by moist obstructive airway sounds, snoring, and progressive rear leg weakness especially noticeable because of the muscle atrophy seen over her Lumbar, Lumbo-Sacral spine and Pelvis, Pelvic limbs. The owners had also noticed a problem with the leaking of urine over the past few years.

The medication selected to treat her polyneuropathy is the sustained release,
semisynthetic opioid agonist, Oxycodone hydrochloride (OxyContin®), 10 mg tablets, given orally every 12 hours.

Within the first six hours after starting the medication, the Lingual, Pharyngeal and Laryngeal Symptoms had all but abated. After the first week on medication all the symptoms of her urinary tract incontinence began to recede. By the 3rd week after starting the medication, most of the muscle mass had returned to the Lumbar, Lumbo-Sacral spine, Pelvis, Pelvic limbs.

For the next several months she stayed on the same dose and frequency of (OxyContin®), 10mg administered every 12 hours. This provided a stable therapeutic blood level, which ameliorated all the symptoms of the aforementioned polyneuropathic syndrome.

Because of the extraordinary high cost of (OxyContin®), the owner elected to change the type of medication to an equivalent amount of the sustained release, opioid agonist, Morphine Sulfate E.R. 15mg/tab, given every 12 hours.

Unfortunately, after just a single week on the new medication, all the previous symptoms of her polyneuropathic syndrome returned. She was again choking, gagging and coughing, having trouble swallowing, showing symptoms of respiratory distress, especially when stressed or when exercising and urine staining was noted in areas where she had been resting or sleeping. The most surprising finding, however, was the almost complete loss of muscle mass over her Lumbo-Sacral Spine and down her Pelvis, Pelvic Limbs which accompanied the return of weakness and incoordination in these areas.

The owner was instructed to stop the Morphine Sulfate E.R. and to immediately begin administration of the previously prescribed dose of (OxyContin®). After 24 hours the owner reported complete return of the laryngeal, pharyngeal, and lingual function. Over the next two weeks the function and muscling of the lumbar, lumbosacral spine, pelvis, pelvic limbs returned, as did the patency of the urinary bladder sphincter.

Example 4

"K.P.", a three year old, neutered, male, Siberian Husky (dog), was medicated with high dose (OxyContin® 40mg am, and 60 mg pm) for the treatment of an inherited form of laryngeal paresis/paralysis. The treatment has been effective in
ameliorating the laryngeal paresis/paralysis.

**Example 5**

"P.J.", a seventeen year old, neutered, male, Belgium Shepard (dog), was medicated with (OxyContin® 10 mg every 12 hours) for the treatment of lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar-lumbo-sacral paresis/paralysis, and pelvis-pelvic limb paresis/paralysis. The treatment has been effective in eliminating or reducing the symptoms of lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, urinary bladder sphincter paresis/paralysis, lumbar-lumbo-sacral paresis/paralysis, and pelvis-pelvic limb paresis/paralysis.

**Example 6**

"M.G.", a thirteen year old, neutered, male, mid-sized, Terrier cross (dog), was initially medicated with (Morphine Sulfate Extended Release 15mg, 1/2 tab every 12 hours), which was replaced by (OxyContin® 10 mg every 12 hours) to treat the symptoms associated with a polyneuropathy which include: lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, and pelvis-pelvic limb paresis/paralysis. The treatment with OxyContin® has been effectively reduced the symptoms of lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, and pelvis-pelvic limb paresis/paralysis.

**Example 7**

"L.G.", a fourteen year old, spayed, female, Golden Retriever (dog), was initially treated with (Morphine Sulfate, Immediate Release, Suspension, 20mg/ml, 5-10 drops every 12 hours), which was replaced with (Oxycodone Extended Release 15mg, 1/2 tab every 12 hours) to treat the symptoms associated with a polyneuropathy which include: lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, and pelvis-pelvic limb paresis/paralysis. The treatment has been effective in reducing the symptoms of the lingual paresis/paralysis, pharyngeal paresis/paralysis, laryngeal paresis/paralysis, and pelvis-pelvic limb paresis/paralysis associated with her neuropathy.
The above examples provide documentation, which support the following:

(1) Pharmaceutical formulations from the group of drugs known as "Opioids" are effective as a treatment which prevents or ameliorates the neurologic/neurogenic symptoms associated with the disorders including Lingual (Paresis/Paralysis), Pharyngeal (Paresis/Paralysis), Laryngeal (Paresis/Paralysis), Esophageal (Paresis/Paralysis), Urinary Bladder Sphincter (Paresis/Paralysis), Lumbar, Lumbo-Sacral Spine (Paresis/Paralysis), and Pelvis, Pelvic Limb (Paresis/Paralysis).

(2) When a subject's Neurologic/Neurogenic symptoms have been ameliorated by the use of a specific pharmaceutical formulation of opioid, substitution of a different, but equivalent pharmaceutical formulation of opioid does not guarantee continued successful treatment of the same symptoms.

(3) Different subjects with similar presenting Neurologic/Neurogenic disorders do not respond the same when treated with the same pharmaceutical formulations of opioids, in the same manner.

Although the invention has been described with reference to the presently preferred embodiments, it should be understood that various modifications can be made without departing from the spirit of the invention. All publications, patents, patent applications, and web sites are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety. The disclosure of each individual publication, patent or patent application is not an admission that each is a prior art reference.
What is claimed is:

1. A method for treating a neurologic or neurogenic disorder comprising administering to a subject in need of such treatment a pharmaceutical formulation comprising a therapeutically effective amount of an opioid compound that prevents, ameliorates or reduces symptoms of said neurologic or neurogenic disorder.

2. The method of claim 1, wherein said neurologic or neurogenic disorder is lingual, pharyngeal, laryngeal, esophageal, urinary bladder sphincter, lumbar-lumbo-sacral spine, or pelvis-pelvic limb paresis or paralysis.

3. The method of claim 2, wherein said subject suffers from one or more of lingual, pharyngeal, laryngeal, esophageal, urinary bladder sphincter, lumbar-lumbo-sacral spine, or pelvis-pelvic limb paresis or paralysis.

4. The method of claim 3, wherein said subject suffers from lingual paresis or paralysis.

5. The method of claim 3, wherein said subject suffers from pharyngeal paresis or paralysis.

6. The method of claim 3, wherein said subject suffers from laryngeal paresis or paralysis.

7. The method of claim 3, wherein said subject suffers from esophageal paresis or paralysis.

8. The method of claim 3, wherein said subject suffers from urinary bladder sphincter paresis or paralysis.

9. The method of claim 3, wherein said subject suffers from lumbar- lumbo-sacral spine paresis or paralysis.
10. The method of claim 3, wherein said subject suffers from one pelvis-pelvic limb paresis or paralysis.

11. The method of claim 1, wherein said opioid compound is a naturally occurring opium alkaloid.

12. The method of claim 11, wherein said naturally occurring opium alkaloid is morphine, codeine, thebaine, papaverine, or noscapine, or a pharmaceutically or veterinarily acceptable salt thereof.

13. The method of claim 1, wherein said opioid compound is a semi-synthetic opium alkaloid.

14. The method of claim 13, wherein said semi-synthetic opium alkaloid is heroin, hydromorphone, metapton, oxymorphone, levorphanol, hydrocodone, oxycodone, tramadol, nalorphine, naloxone, or naltrexone, or a pharmaceutically or veterinarily acceptable salt thereof.

15. The method of claim 1, wherein said opioid compound is a synthetic opium alkaloid.

16. The method of claim 12, wherein said synthetic opium alkaloid is meperidine and congeners, methadone and congeners, levorphanol and congeners, phenazocine, fentanyl, propoxyphene and ethoheptazine, or a pharmaceutically or veterinarily acceptable salt thereof.

17. The method of claim 1, wherein said pharmaceutical formulation has said opioid compound is in an immediate or sustained release form.

18. The method of claim 1, wherein said pharmaceutical formulation further comprises a pharmaceutically or veterinarily acceptable carrier.

19. The method of claim 1, wherein said pharmaceutical formulation is
administered about no more than eight times within a twenty-four hour period.

20. The method of claim 1, wherein said pharmaceutical formulation is administered to the subject in a daily dose range of about 0.1 mg to 200 mg.

21. The method of claim 20, wherein said pharmaceutical formulation is administered to the subject in a daily dose range of about 1 mg to 100 mg.

22. The method of claim 1, wherein said pharmaceutical formulation is administered orally, intravenously, intramuscularly, subcutaneously, or transdermally.

23. The method of claim 1, wherein the subject is a mammal.

24. The method of claim 23, wherein the subject is a non-human mammal.

25. The method of claim 23, wherein the subject is a human.

26. Use of an opioid compound having an amount effective to reduce paresis or paralysis in the manufacturer of a medicament for use in a method of treating a neurologic or neurogenic disorder in a subject in need of such treatment, wherein said medicament is administered in an amount sufficient to prevent, ameliorate or reduce the symptoms of said neurologic or neurogenic disorder in said subject.

27. The use of claim 26, wherein said neurologic or neurogenic disorder is lingual, pharyngeal, laryngeal, esophageal, urinary bladder sphincter, lumbar-lumbo-sacral spine, or pelvis-pelvic limb paresis or paralysis.

28. The use of claim 27, wherein said subject suffers from one or more of lingual, pharyngeal, laryngeal, esophageal, urinary bladder sphincter, lumbar-lumbo-sacral spine, or pelvis-pelvic limb paresis or paralysis.

29. The use of claim 28, wherein said subject suffers from lingual paresis or
paralysis.

30. The use of claim 28, wherein said subject suffers from pharyngeal paresis or paralysis.

31. The use of claim 28, wherein said subject suffers from laryngeal paresis or paralysis.

32. The use of claim 28, wherein said subject suffers from esophageal paresis or paralysis.

33. The use of claim 28, wherein said subject suffers from urinary bladder sphincter paresis or paralysis.

34. The use of claim 28, wherein said subject suffers from lumbar-lumbo-sacral spine paresis or paralysis.

35. The use of claim 28, wherein said subject suffers from one pelvis-pelvic limb paresis or paralysis.

36. The use of claim 26, wherein said opioid compound is a naturally occurring opium alkaloid.

37. The use of claim 36, wherein said naturally occurring opium alkaloid is morphine, codeine, thebaine, papaverine, or noscapine, or a pharmaceutically or veterinarily acceptable salt thereof.

38. The use of claim 26, wherein said opioid compound is a semi-synthetic opium alkaloid.

39. The use of claim 38, wherein said semi-synthetic opium alkaloid is heroin, hydromorphone, metapone, oxymorphone, levorphanol, hydrocodone, oxycodone, tramadol, nalorphine, naloxone, or naltrexone, or a pharmaceutically or veterinarily
acceptable salt thereof.

40. The use of claim 39, wherein said opioid compound is a synthetic opium alkaloid.

41. The use of claim 40, wherein said synthetic opium alkaloid is meperidine and congers, methadone and congeners, levorphanol and congeners, phenazocine, fentanyl, propoxyphene and ethoheptazine, or a pharmaceutically or veterinarily acceptable salt thereof.

42. The use of claim 26, wherein said pharmaceutical formulation has said opioid compound is in an immediate or sustained release form.

43. The use of claim 26, wherein said pharmaceutical formulation further comprises a pharmaceutically or veterinarily acceptable carrier.

44. The use of claim 26, wherein said pharmaceutical formulation is administered about no more than eight times within a twenty-four hour period.

45. The use of claim 26, wherein said pharmaceutical formulation is administered to the subject in a daily dose range of about 0.1 mg to 200 mg.

46. The use of claim 45, wherein said pharmaceutical formulation is administered to the subject in a daily dose range of about 1 mg to 100 mg.

47. The use of claim 26, wherein said pharmaceutical formulation is administered orally, intravenously, intramuscularly, subcutaneously, or transdermally.

48. The use of claim 26, wherein the subject is a mammal.

49. The use of claim 48, wherein the subject is a non-human mammal.

50. The use of claim 48, wherein the subject is a human.
51. A method for testing or identifying an opioid compound or a pharmaceutical formulation capable of preventing, ameliorating, reducing or curing a neurologic or neurogenic disorder or syndrome, comprising:

(a) determining the function of an organ of a subject, wherein said subject suffers from a neurologic or neurogenic disorder or syndrome,

(b) administering said opioid compound or said pharmaceutical formulation to said subject,

(c) determining the function of said organ of said subject, and

(d) identifying said opioid compound or said pharmaceutical formulation wherein said function determined in step (c) is prevented, ameliorated, reduced or cured compared to said function determined in step (a).

52. The method of Claim 51, wherein the function of said organ is neurologic or neurogenic lingual, pharyngeal, laryngeal, esophageal, urinary bladder sphincter, lumbar-lumbo-sacral spine, or pelvis-pelvic limb control or function.

53. The method of Claim 51, wherein the step of determining the function of an organ is grading the function using a grading system.

54. The method of Claim 51, wherein the opioid compound tested is an unknown opioid compound.