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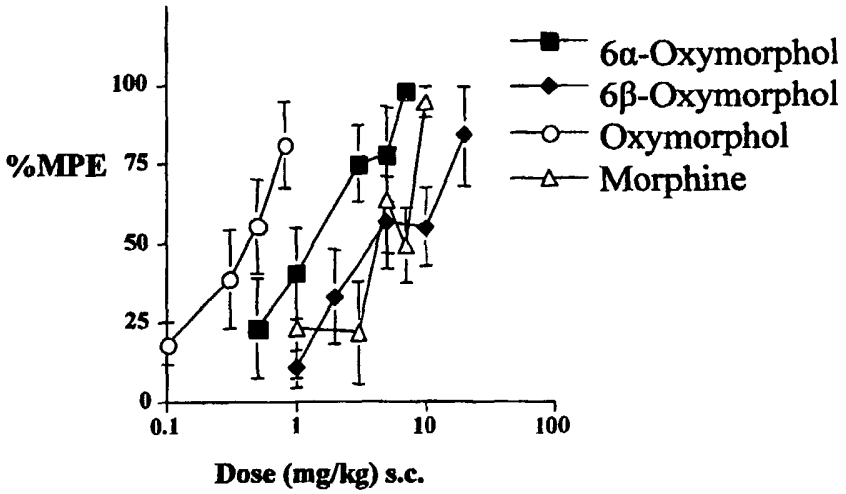
(54) Title: 6 α-OXYMORPHOL AND A METHOD OF USE



(57) Abstract: A composition comprising optically pure 6α-oxymorphol is disclosed. Also disclosed is a method of treating pain, in a patient in need of pain relief, by administering to the individual an amount of optically pure 6α-oxymorphol or a pharmaceutically acceptable salt thereof sufficient to cause analgesia. The method is particularly useful in treating pain while reducing the amount of opioid given to a patient.

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6 α-OXYMORPHOL AND A METHOD OF USE

DESCRIPTION

1. Background

The present invention relates to analgesics, and specifically to opioid analgesics.

Oxymorphol, the metabolite of oxymorphone, is a drug belonging to the general class of opioid analgesic compounds. The prime action of opioid analgesic drugs is to stimulate the opioid receptor, thereby producing analgesia.

Oxymorphone (14-hydroxydihydromorphinone) is indicated for the treatment of moderate-to-severe pain. Oxymorphone is a semisynthetic opioid agonist derived from thebaine, with a significantly higher analgesic potency than that of morphine. Its structure is related to morphine, differing in a ketone group substitution at the C-6 position of morphine and saturation of the 7-8 double-bond. In addition, oxymorphone has a hydroxyl group on the saturated hexane ring. The ketone group substitution makes the molecule more lipid soluble, conferring greater potency and more rapid onset of action than the hydroxylated, structurally-related compound morphine.

Oxymorphol ("6-hydroxyoxymorphone" or "6-OH oxymorphone") is oxymorphone which has been hydroxylated at the 6- position. This hydroxylation occurs *in vivo* in humans after administration of oxymorphone, and the oxymorphone metabolite, oxymorphol, is formed. Oxymorphol as a metabolite of oxymorphone is well known (see for example, Cone et al., 1983 Metabolism and Disposition vol. 11, pp 446-450). It has recently been found that oxymorphol is an active metabolite and not only binds the opioid receptor but also causes analgesia. US patent publication US2003130297 discloses this administration of oxymorphol to achieve analgesia. Oxymorphol is believed to achieve analgesia according to the same mechanism as morphine or other opioids. That is, oxymorphol stimulates an opioid receptor to achieve analgesia.

The 6-hydroxylation substitution of oxymorphone is made through selective reduction of the ketone group of the oxymorphone molecule *in vivo*, which results in two enantiomers, 6α-oxymorphol and 6β-oxymorphol. Because *in vivo* production is not stereo-specific, oxymorphol is formed *in vivo* as a mixture of optical isomers, or enantiomers. The degree of reduction of urinary oxymorphone of 6α-oxymorphol or 6β-oxymorphol is variable across species, but 6α remains below detectable limits or consistently low in all species relative to 6β (Cone et al., 1983 Metabolism and Disposition vol 11, pp 446-450). Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the

other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Many biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to optically pure 6α-oxymorphol, as well as a method of treating pain, in a patient in need of pain relief, by administering to the patient an amount of optically pure 6α-oxymorphol or a pharmaceutically acceptable salt thereof sufficient to cause analgesia, while minimizing side effects associated with 6β-oxymorphol, the primary enantiomer of oxymorphol. The method is particularly useful in treating pain while reducing the amount of opioid given to a patient. In these applications, it is important to have a composition which is a potent analgesic and which minimizes the adverse side effects of opioids by reducing the dosage amount by eliminating the 6β enantiomer. A composition containing the pure 6α- isomer of oxymorphol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating pain while reducing the amount of opioid administered.

BRIEF DESCRIPTION OF THE FIGURES

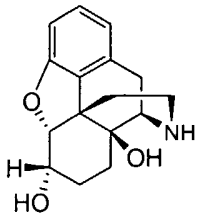
Figure 1 is a graph of the results of a tail-flick assay in rats showing relative potency of several opioids.

Figure 2 is a graph of the results of a hot plate assay in rats showing relative potency of several opioids.

Figure 3 is a graph of the number of abdominal constrictions in a mouse phenylquinone writhing model test.

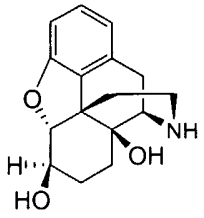
DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the analgesic activity of the 6α- enantiomer of oxymorphol to provide analgesia, while simultaneously reducing the amount of opioid administered to oxymorphol users. In the present method, the optically pure 6α- isomer of oxymorphol, which is substantially free of the 6β- enantiomer, is administered alone, or in combination with one or more other active pharmaceutical ingredients (APIs) in adjunctive treatment, to an individual in whom pain relief is desired. The optically pure 6α- isomer of oxymorphol as used herein refers to the levorotatory optically pure isomer of 6,14 dihydroxy, dihydromorphinone (Formula I) and to any pharmacologically acceptable salt or ester thereof.



6 alpha oxymorphol

Formula I



6 beta oxymorphol

Formula II

The 6α and 6β forms of oxymorphol were tested to determine relative binding to opioid receptors. Both enantiomers exhibited characteristic opioid binding. The binding of the two enantiomers to opioid receptors was similar. This indicates that the potency of the two enantiomers should be similar. However, it has been discovered that 6α-oxymorphol is surprisingly more potent than 6β-oxymorphol. Depending on the test, 6α-oxymorphol is between 3 and 8 times more potent than 6β-oxymorphol. This is completely unexpected based on very similar binding properties of the two enantiomers. In addition, since the α enantiomer is either not detectable or found in vanishing small concentrations (Cone et al., 1983 Metabolism and Disposition vol 11, pp 446-450), it would not be expected to contribute to the analgesic efficacy of either oxymorphone or the 6α, 6β mixture of oxymorphol, produced as a metabolite in humans.

The 6α- isomer of the present invention oxymorphol is administered to an individual in need of analgesia. For example, 6α-oxymorphol is administered to an individual before pain is experienced (as with surgical pain), or after the onset of pain. Such pain may be may be of any origin and any type, including nociceptive, somatic, or neuropathic. Such pain may be acute, as from an accident, or it may be chronic, as from cancer or a permanent injury. In another embodiment, optically pure 6α-oxymorphol is administered prophylactically, that is, before the pain begins, as with surgery, to prevent its occurrence or to reduce the extent to which it occurs.

The 6α-oxymorphol the present invention can be administered by any acceptable route of administration of an opioid. These routes include, but are not limited to injection (whether intrathecal, intramuscular, intravenous, subcutaneous or other), oral, topical, parenteral, nasal, transdermal, rectal, sublingual or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., tablet, capsule, solution, emulsion) will depend on the route by which it is administered. Furthermore, the dosage form used will also depend on the intended duration of analgesia, and may include immediate-release or extended release dosage forms. The quantity of the drug to be administered will be determined on an

individual basis, and will be based, at least in part, on consideration of the patient's size, whether the patient is opioid naïve, the severity of the symptoms to be treated, the duration of action desired, and the result sought. In general, quantities of optically pure 6α-oxymorphol sufficient to reduce or eliminate a patient's pain will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by injection or oral administration. As with any opioid, the smallest effective dose to relieve pain should be administered. Doses as small as .01 mg/kg or as high as about 10 mg/kg of the optically pure 6α- isomer of oxymorphol given every four hours will generally be adequate to produce the desired analgesic effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 160 mg two to four times daily is administered to produce the desired effect. For parenteral administration, similar quantities are given on the same schedule (i.e. about 1 mg to about 160 mg two to four times daily). The compound of the present invention can also be administered in any other route normally used for administration of opioids, including (but not limited to) buccal, transdermal, intranasal, or sublingual administration. Furthermore, extended release formulations, intended for twice, or once-daily administration may contain two to four times the dose of an immediate release formulation referred to above. Devices, such as implantable pumps, or transdermal patches, may contain many times the 6α-oxymorphol than that of oral or parenteral dosage forms for use over extended periods of from one day to one month, or longer.

In the method of the present invention, the optically pure 6α- isomer of oxymorphol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine can be given with or in close temporal proximity to administration of optically pure, 6α-oxymorphol. Additionally, a combination can be administered which includes 6α-oxymorphol and an NSAID such as aspirin, ibuprofen, ketoprofen or naproxen, a COX-2 inhibitor including celecoxib or rofecoxib, or another analgesic such as acetaminophen. The two (or more) active pharmaceutical ingredients (APIs) (the optically pure active isomer of oxymorphol and another API) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure 6α-oxymorphol and one or more other APIs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalant form can include, in addition to the APIs, a liquid carrier and/or propellant. A

composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent, a lubricant, and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent. These are intended to be only non-limiting examples of excipients which may be used in conjunction with the pharmaceutical ingredient of the present invention.

In general, according to the method of the present invention, the optically pure 6α- isomer of oxymorphol, or a pharmaceutically acceptable salt thereof, alone or in combination with one or more other APIs, is administered to an individual periodically as necessary to reduce pain. The present composition and method provide an effective treatment for pain while minimizing the undesirable side effects associated with oxymorphol use. These side effects include central nervous system depression, nausea, constipation, and vomiting.

The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. Suitable acids for pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, ascorbic, benzenesulfonic (besylate), benzoic, boric, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, glutaric, glycerophosphoric, hydrobromic, hydrochloric, hydroiodic, isethionic, lactic, maleic, malic, malonic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, salicylic, succinic, sulfuric, tartaric acid, terephthalic, p-toluenesulfonic, and the like. When a compound contains an acidic side chain, suitable pharmaceutically acceptable base addition salts include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine.

Suitable pharmaceutically acceptable salts also include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-.beta.-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine,

glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

The terms "optically pure" or "substantially free of the 6β- enantiomer" as used herein means that in a composition, at least 75% by weight of the oxymorphol in the composition is the 6α- isomer (Formula I) of oxymorphol and 25% by weight or less is the 6β- isomer (Formula II). Preferably, of the oxymorphol in the composition, at least 90% by weight is the 6α- isomer of oxymorphol and 5% by weight or less in the 6β- isomer. More preferably, at least 95% by weight is the 6α- isomer of oxymorphol and 5% by weight or less is the 6β- isomer. More preferably, of the oxymorphol in the composition, at least 99% by weight is the 6α- isomer of oxymorphol and 1% by weight or less is the 6β- isomer. Optically pure oxymorphol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate, or by chiral separation from the racemate.

Another aspect of the subject invention is compositions which comprise a safe and effective amount of 6α- oxymorphol, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable carrier. As used herein, "safe and effective amount" means an amount of the subject compound sufficient to induce analgesia, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A safe and effective amount of the subject compound will vary with the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

Compositions of the subject invention preferably comprise from about 0.0001% to about 99% by weight of the subject compound, more preferably from about 0.01% to about 90%; also preferably from about 0.1% to about 50%, also preferably from about 1% to about 25%, and also preferably from about 5% to about 10%.

In addition to the subject compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of

course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or animal being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as Tween; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is generally determined by the way the compound is to be administered. For instance, if the subject compound is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with blood-compatible suspending agent, the pH of which has been adjusted to about 7.4. Other modes of administration will be familiar to those skilled in the art, as will the preferred pharmaceutically-acceptable carrier for each.

The preferred modes of administering the subject compound are oral and parenteral. The preferred unit dosage forms are therefore tablets, capsules, lozenges, chewable tablets, orally disintegratable tablets, sublingual tablets, buccal tablets, solutions, emulsions, suspensions, and the like. Such unit dosage forms comprise a safe and effective amount of the subject compound, which for immediate release dosage forms is preferably from about 0.01 mg to about 200 mg, more preferably from about 0.1 mg to about 100 mg, more preferably still from about 0.5 mg to about 25 mg, also preferably from about 1 mg to about 25 mg, also preferably from about 5 mg to about 10 mg. Controlled (or extended) release dosage forms would have commensurately more of the subject compound, depending on the dosing schedule. For a twice daily dosing, the amount of the subject compound would be double to triple the ranges above, whereas for once daily dosing, four to six times the amounts set forth above would typically be used.

The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium

carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art.

Oral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Such liquid oral compositions preferably comprise from about 0.001% to about 5% of the subject compound, more preferably from about 0.01% to about 0.5%. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Oral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Other compositions useful for attaining systemic delivery of the subject compound include sublingual and buccal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included. Such dosage forms may also include foaming or gas-generating agents, such as sodium carbonate and ascorbic acid.

Preferred compositions of the subject invention include solids, such as tablets and capsules, and liquids, such as solutions, suspensions, and emulsions (preferably in soft gelatin capsules), comprising a safe and effective amount of a subject compound intended for administration via the gastrointestinal tract by oral administration. Such compositions intended for four-hour administration preferably comprise from about 0.01 mg to about 100 mg per dose, more preferably from about 0.1 mg to about 50 mg per dose. Such

compositions can be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released over time to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, acrylic coatings, polyvinylpyrrolidone, waxes and shellac. Such dosage also typically include several times as much of the subject compound as noted above.

Compositions of the subject invention may optionally include other active pharmaceutical ingredients. Non-limiting examples of APIs which may be incorporated in these compositions, include: antihistamines, including; hydroxyzine preferably at a dosage range of from about 25 to about 400 mg; doxylamine, preferably at a dosage range of from about 3 to about 75 mg; pyrilamine, preferably at a dosage range of from about 6.25 to about 200 mg; chlorpheniramine, preferably at a dosage range of from about 1 to about 24 mg; phenindamine, preferably at a dosage range of from about 6.25 to about 150 mg; dexchlorpheniramine, preferably at a dosage range of from about 0.5 to about 12 mg; dexbrompheniramine, preferably at a dosage range of from about 0.5 to about 12 mg; clemastine, preferably at a dosage range of from about 1 to about 9 mg; diphenhydramine, preferably at a dosage range of from about 6.25 to about 300 mg; azelastine, preferably at a dosage range of from about 140 to about 1,680 μg (when dosed intranasally), 1 to about 8 mg (when dosed orally); acrivastine, preferably at a dosage range of from about 1 to about 24 mg; levocarbastine (which can be dosed as an intranasal or ocular medicament), preferably at a dosage range of from about 100 to about 800 μg; mequitazine, preferably at a dosage range of from about 5 to about 20 mg; astemizole, preferably at a dosage range of from about 5 to about 20 mg; ebastine; loratadine, preferably at a dosage range of from about 5 to about 40 mg; cetirizine, preferably at a dosage range of from about 5 to about 20 mg; terfenadine, preferably at a dosage range of from about 30 to about 480 mg; terfenadine metabolites; promethazine, preferably at a dosage range of from about 6.25 to about 50 mg; dimenhydrinate, preferably at a dosage range of from about 12.5 to about 400 mg; meclizine, preferably at a dosage range of from about 6.25 to about 50 mg; tripelennamine, preferably at a dosage range of from about 6.25 to about 300 mg; carbinoxamine, preferably at a dosage range of from about 0.5 to about 16 mg; cyproheptadine, preferably at a dosage range of from about 2 to about 20 mg; azatadine, preferably at a dosage range of from about 0.25 to about 2 mg; brompheniramine, preferably at a dosage range of from about 1 to about 24 mg; triprolidine, preferably at a dosage range of from about 0.25 to about 10 mg; cyclizine, preferably at a dosage range of from about 12.5 to about 200 mg; thonzylamine, preferably at

a dosage range of from about 12.5 to about 600 mg; pheniramine, preferably at a dosage range of from about 3 to about 75 mg; dextromethorphan, preferably at a dosage range of from about 2.5 to about 120 mg; noscapine, preferably at a dosage range of from about 3 to about 180 mg; benzonatate, preferably at a dosage range of from about 100 to about 600 mg; diphenhydramine, preferably at a dosage range of from about 12.5 to about 150 mg; chlophedianol, preferably at a dosage range of from about 12.5 to about 100 mg; clobutinol, preferably at a dosage range of from about 20 to about 240 mg; fominoben, preferably at a dosage range of from about 80 to about 480 mg; glaucine; pholcodine, preferably at a dosage range of from about 1 to about 40 mg; zipeprol, preferably at a dosage range of from about 75 to about 300 mg; hydromorphone, preferably at a dosage range of from about 0.5 to about 8 mg; carbetapentane, preferably at a dosage range of from about 15 to about 240 mg; caramiphen, levopropoxyphene, preferably at a dosage range of from about 25 to about 200 mg and others; anti-inflammatories, preferably non-steroidal anti-inflammatories, (NSAIDS) including; ibuprofen, preferably at a dosage range of from about 50 to about 3,200 mg; naproxen, preferably at a dosage range of from about 62.5 to about 1,500 mg; sodium naproxen, preferably at a dosage range of from about 110 to about 1,650 mg; ketoprofen, preferably at a dosage range of from about 25 to about 300 mg; indoprofen, indomethacin, preferably at a dosage range of from about 25 to about 200mg; sulindac, preferably at a dosage range of from about 75 to about 400 mg; diflunisal, preferably at a dosage range of from about 125 to about 1,500 mg; ketorolac, preferably at a dosage range of from about 10 to about 120 mg; piroxicam, preferably at a dosage range of from about 10 to about 40 mg; aspirin, preferably at a dosage range of from about 80 to about 4,000 mg; meclofenamate, preferably at a dosage range of from about 25 to about 400 mg; benzydamine, preferably at a dosage range of from about 25 to about 200 mg; carprofen, preferably at a dosage range of from about 75 to about 300 mg; diclofenac, preferably at a dosage range of from about 25 to about 200 mg; etodolac, preferably at a dosage range of from about 200 to about 1,200 mg; fenbufen, preferably at a dosage range of from about 300 to about 900 mg; fenoprofen, preferably at a dosage range of from about 200 to about 3,200 mg; flurbiprofen, preferably at a dosage range of from about 50 to about 300 mg; mefenamic acid, preferably at a dosage range of from about 250 to about 1,500 mg; nabumetone, preferably at a dosage range of from about 250 to about 2,000 mg; phenylbutazone, preferably at a dosage range of from about 100 to about 400 mg; pirprofen, preferably at a dosage range of from about 100 to about 800 mg; tolmetin, preferably at a dosage range of from about 200 to about 1,800 mg and others; analgesics, including; acetaminophen, preferably at a dosage range of from about

80 to about 4,000 mg; and others: expectorants/mucolytics, including; guaifenesin, preferably at a dosage range of from about 50 to about 2,400mg; n-acetylcysteine, preferably at a dosage range of from about 100 to about 600 mg; ambroxol, preferably at a dosage range of from about 15 to about 120 mg; bromhexine, preferably at a dosage range of from about 4 to about 64 mg; terpin hydrate, preferably at a dosage range of from about 100 to about 1,200 mg; potassium iodide, preferably at a dosage range of from about 50 to about 250 mg and others; atropinics, preferably intranasally or orally administered atropinics, including; ipratroprium (preferably intranasally), preferably at a dosage range of from about 42 to about 252 μg; atropine sulfate (preferably oral), preferably at a dosage range of from about 10 to about 1,000 μg; belladonna (preferably as an extract), preferably at a dosage range of from about 15 to about 45 mg equivalents; scopolamine, preferably at a dosage range of from about 400 to about 3,200 μg; scopolamine methobromide, preferably at a dosage range of from about 2.5 to about 20 mg; homatropine methobromide, preferably at a dosage range of from about 2.5 to about 40 mg; hyoscyamine (preferably oral), preferably at a dosage range of from about 125 to about 1,000 μg; isopropramide (preferably oral), preferably at a dosage range of from about 5 to about 20 mg; orphenadrine (preferably oral), preferably at a dosage range of from about 50 to about 400 mg; benzalkonium chloride (preferably intranasally) preferably a 0.005 to about 0.1% solution and others; mast cell stabilizers, preferably intranasally, or orally administered mast cell stabilizers, including; cromalyn, preferably at a dosage range of from about 10 to about 60 mg; nedocromil, preferably at a dosage range of from about 10 to about 60 mg; oxatamide, preferably at a dosage range of from about 15 to about 120 mg; ketotifen, preferably at a dosage range of from about 1 to about 4 mg; lodoxamide, preferably at a dosage range of from about 100 to about 3,000 μg and others; LT Antagonists, including zileuton and others; methylxanthines, including; caffeine, preferably at a dosage range of from about 65 to about 600 mg; theophyllene, preferably at a dosage range of from about 25 to about 1,200 mg; enprofylline; pentoxifylline, preferably at a dosage range of from about 400 to about 3,600 mg; aminophylline, preferably at a dosage range of from about 50 to about 800 mg; dyphylline, preferably at a dosage range of from about 200 to about 1,600 mg and others; antioxidants or radical inhibitors, including; ascorbic acid, preferably at a dosage range of from about 50 to about 10,000 mg; tocopherol, preferably at a dosage range of from about 50 to about 2,000 mg; ethanol, preferably at a dosage range of from about 500 to about 10,000 mg and others; steroids, preferably intranasally administered steroids, including: beclomethasone, preferably at a dosage range of from about 84 to about 336 μg; fluticasone, preferably at a dosage range of from about 50 to about 400 μg; budesonide, preferably at a

dosage range of from about 64 to about 256 μg; mometasone; triamcinolone, preferably at a dosage range of from about 110 to about 440 μg; dexamethasone, preferably at a dosage range of from about 168 to about 1,008 μg; flunisolide, preferably at a dosage range of from about 50 to about 300 μg; prednisone (preferably oral), preferably at a dosage range of from about 5 to about 60 mg; hydrocortisone (preferably oral), preferably at a dosage range of from about 20 to about 300 mg and others; bronchodilators, preferably for inhalation, including; albuterol, preferably at a dosage range of from about 90 to about 1,080 μg; 2 to about 16 mg (if dosed orally); epinephrine, preferably at a dosage range of from about 220 to about 1,320 μg; ephedrine, preferably at a dosage range of from about 15 to about 240 mg (if dosed orally); 250 to about 1,000 μg (if dosed intranasally); metaproterenol, preferably at a dosage range of from about 65 to about 780 μg or 10 to about 80 mg if dosed orally; terbutaline, preferably at a dosage range of from about 200 to about 2,400 μg; 2.5 to about 20 mg if dosed orally; isoetharine, preferably at a dosage range of from about 340 to about 1,360 μg; pirbuterol, preferably at a dosage range of from about 200 to about 2,400 μg; bitolterol, preferably at a dosage range of from about 370 to about 2,220 μg; fenoterol, preferably at a dosage range of from about 100 to about 1,200 μg; 2.5 to about 20 mg (if dosed orally); rimeterol, preferably at a dosage range of from about 200 to about 1,600 μg; ipratroprium, preferably at a dosage range of from about 18 to about 216 μg (inhalation) and others; and antivirals, including; amantadine, preferably at a dosage range of from about 50 to about 200 mg; rimantadine, preferably at a dosage range of from about 50 to about 200 mg; enviroxime; nonoxinols, preferably at a dosage range of from about 2 to about 20 mg (preferably an intranasal form); acyclovir, preferably at a dosage range of from about 200 to about 2,000 mg (oral); 1 to about 10 mg (preferably an intranasal form); alpha-interferon, preferably at a dosage range of from about 3 to about 36 MIU; beta-interferon, preferably at a dosage range of from about 3 to about 36 MIU and others; ocular drug actives: acetylcholinesterase inhibitors, e.g., echothiophate from about 0.03% to about 0.25% in topical solution and others; and gastrointestinal actives: antidiarrheals, e.g., ioperamide from about 0.1 mg to about 1.0 mg per dose, and bismuth subsalicylate from about 25 mg to about 300 mg per dose and others. Of course, clearly contemplated and included in the description above are the acid or base addition salts, esters, metabolites of these preferred actives, as well as analogues to these actives that are safe and effective. It is also recognized that an active may be useful for more than one of the above uses, and these uses are clearly contemplated as well. This overlap is recognized in the art and adjusting dosages and the like to fit the indication is well within the purview of the skilled medical practitioner.

EXPERIMENTAL

Non-clinical pharmacology studies were conducted *in vivo* in mice, and using *in vitro* opioid receptor binding assays, in order to more fully describe the action of 6α-oxymorphol and 6β-oxymorphol in the production of analgesia. First, a standard screening assay was used to profile the receptor binding selectivity for each enantiomers against different receptor subtypes, μ, κ and δ. These assays were performed to determine the opioid receptor subtypes for which these compounds exhibit activity.

Both enantiomers exhibited binding characteristics expected of an opioid. Oxymorphone and 6-hydroxyoxymorphone and morphine also exhibit binding activity at each of these three opioid receptor subtypes.

Each of 6α-oxymorphol and 6β-oxymorphol were also tested against a battery of different non-opioid receptor subtypes classified as either transmitter-related, ion channels, or brain gut peptide receptors. No activity was detected at ≤1 μM, indicating a high degree of opioid receptor binding specificity for both enantiomers.

Both enantiomers exhibited equivalent exclusive binding selectivity and affinity for each of the opioid receptor subtypes; that is, no other receptors in a NovaScreen profile of different classes of receptors exhibited affinity for either enantiomer of 6-hydroxyoxymorphone. Table 1 shows the binding affinity (Ki and IC_{50}) for each of the opioid receptor subtypes (selectivity) exhibited by either the 6α-oxymorphol or 6β-oxymorphol enantiomer.

Table 1:

6α-oxymorphol	6β-oxymorphol
Ki/IC_{50} (nM)	Ki/IC_{50} (nM)
μ: 4.2/11	μ: 3.1/8.3
K: 790/1777	K: 430/997
δ: >1700/	δ: 1700/

The receptor binding profiles were similar for both the 6α and 6β enantiomers, indicating that *in vivo* analgesic activity should be similar.

The initial non-clinical *in vivo* pharmacology studies were conducted with oxymorphone, morphine and 6α-oxymorphol and 6β-oxymorphol. The assays used were standard analgesic assays used to detect opioid narcotics in mice and were used to assess relative analgesic potency between compounds: these were tail flick (TF), hot plate (HP) and phenylquinone writhing (PQW). The studies are summarized in Table 2 and in Figures 1-3. Table 2 shows

the ED_{50}s derived for morphine, oxymorphone and the enantiomers of 6-hydroxyoxymorphone from the mouse tail flick and hot plate nociceptive pain assays.

Table 2

Drug	TF (ED_{50}; mg/kg)	HP (ED_{50}; mg/kg)	Writhing (ED_{50}; mg/kg)
Morphine	4.2	5.5	5.0
6α-oxymorphol	1.4	1.0	0.5
6β-oxymorphol	5.1	8.8	1.4
Oxymorphone	0.36	0.31	-

Figures 1 and 2 show the results of these tests. Figure 1 shows a graph of the results of a tail-flick assay in rats given different subcutaneous doses of oxymorphone or either of the two enantiomers of its primary metabolite, 6α-oxymorphol or 6β-oxymorphol. Morphine was included as a reference control for assay sensitivity. There were six rats per dose. Latency to tail withdrawal scores are given by percent maximum possible effect as derived from %MPE = (score – baseline) /baseline X 100 with standard error.

Figure 2 shows a graph of the results of a hot-plate assay in rats given different subcutaneous doses of oxymorphone or either of its two enantiomers of its primary metabolite, oxymorphol. Morphine was included as a reference control for assay sensitivity. There were six rats per dose. Latency to tail withdrawal scores are given by percent maximum possible effect as derived from %MPE = (score – baseline) /baseline X 100 with standard error.

When given at equivalent doses, the 6α enantiomer exhibited significantly greater analgesic activity across all analgesic assays in the mouse. The 6α enantiomer of 6-hydroxyoxymorphone was more potent than the 6β enantiomer in the tail flick and the hot plate model as well as in the phenylquinone writhing test. The 6α-oxymorphol or 6β-oxymorphol or oxymorphone or morphine were given at doses between 0.1 and 10 mg/kg s.c. (subcutaneous) or orally as indicated in the figures. Considering the similar receptor binding profiles of the two compounds, it would be expected that *in vivo* analgesic activity of enantiomers should be similar. The finding of a difference in the analgesic activity of the two compounds was surprising and unexpected.

Figure 3 shows the number of abdominal constrictions in a mouse phenylquinone writhing (PQW) model. The number of constrictions is diminished by morphine (5mg/kg) or by 6α-oxymorphol (2-5mg/kg) or by 6β-oxymorphol (5-10mg/kg). Drugs were given orally. This data shows that for the same dose (5 mg/kg) of enantiomer, the 6α enantiomer produced

fewer writhes in a 10-minute interval than did either morphine or the 6β enantiomer. From the hot plate and tail flick assays as well as the PQW assay, the 6α enantiomer is clearly and surprisingly more potent than the 6β enantiomer.

Taken together this data shows that even with binding data indicating similar affinity and selectivity for the opioid receptor subtypes, and although the 6α enantiomer is reported to be a minor metabolite or below the limit of detection in some species, the 6α enantiomer unexpectedly resulted in analgesic superiority when compared to the 6β enantiomer in standard animal models of pain.

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

What is claimed is:

1. A composition comprising optically pure 6α-oxymorphol or a pharmaceutically acceptable salt thereof.

2. The composition of claim 1 wherein at least 90% by weight of the oxymorphol or salt thereof in the composition is the 6α- isomer of oxymorphol and not more than 10% by weight is the 6β- isomer.

3. A pharmaceutical formulation for oral administration comprising optically pure 6α-oxymorphol or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

4. The formulation of claim 3 wherein at least 90% by weight of the oxymorphol or salt thereof in the formulation is the 6α- isomer of oxymorphol and not more than 10% by weight is the 6β- isomer.

5. A method of treating pain in an individual with oxymorphol, while reducing side effects associated with administration of racemic oxymorphol, comprising administering to the individual a pharmaceutically acceptable formulation containing a quantity of an optically pure 6α- isomer of oxymorphol or a pharmaceutically acceptable salt thereof sufficient to result in pain reduction.

6. The method of claim 5 wherein at least 90% by weight of the oxymorphol or salt thereof in the formulation is the 6α- isomer of oxymorphol and not more than 10% by weight is the 6β-isomer.

7. The method of claim 6 wherein at least 99% by weight of the oxymorphol or salt thereof in the formulation is the 6α- isomer of oxymorphol and 1% by weight or less is the 6β- isomer.

8. A method of claim 5 comprising orally administering to the individual from approximately 10 mg to approximately 500 mg of the 6α- isomer of oxymorphol or a pharmaceutically acceptable salt thereof once daily.

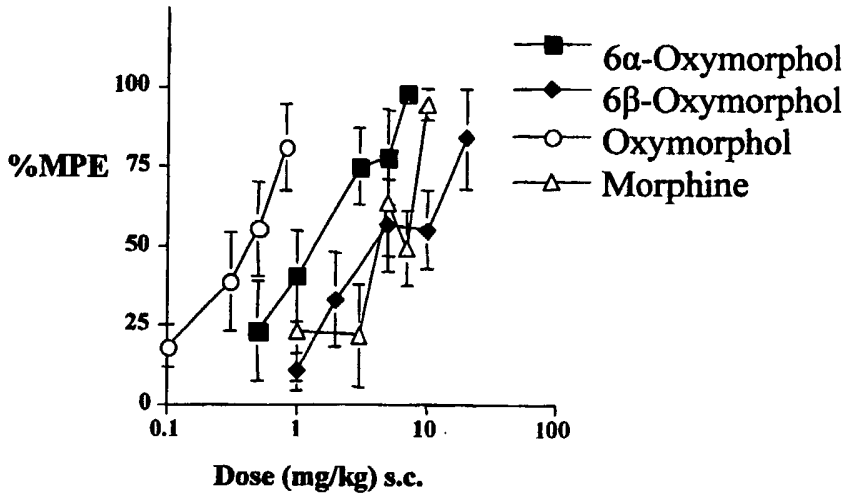


FIGURE 1

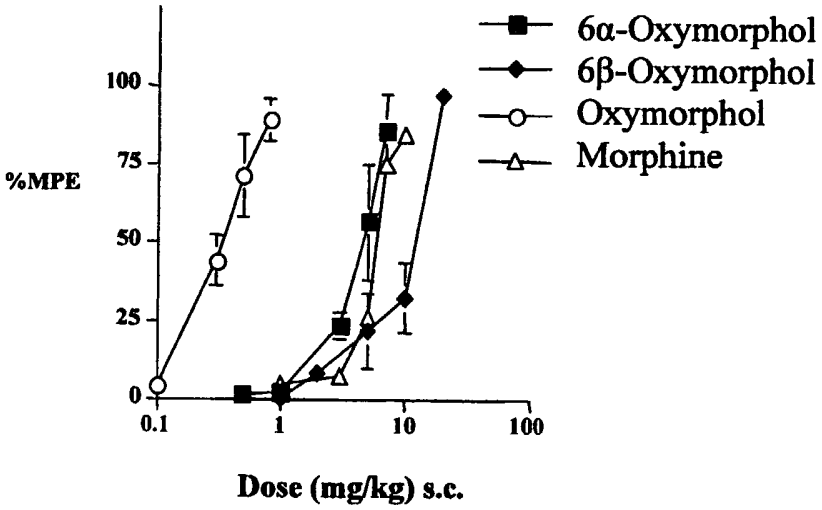
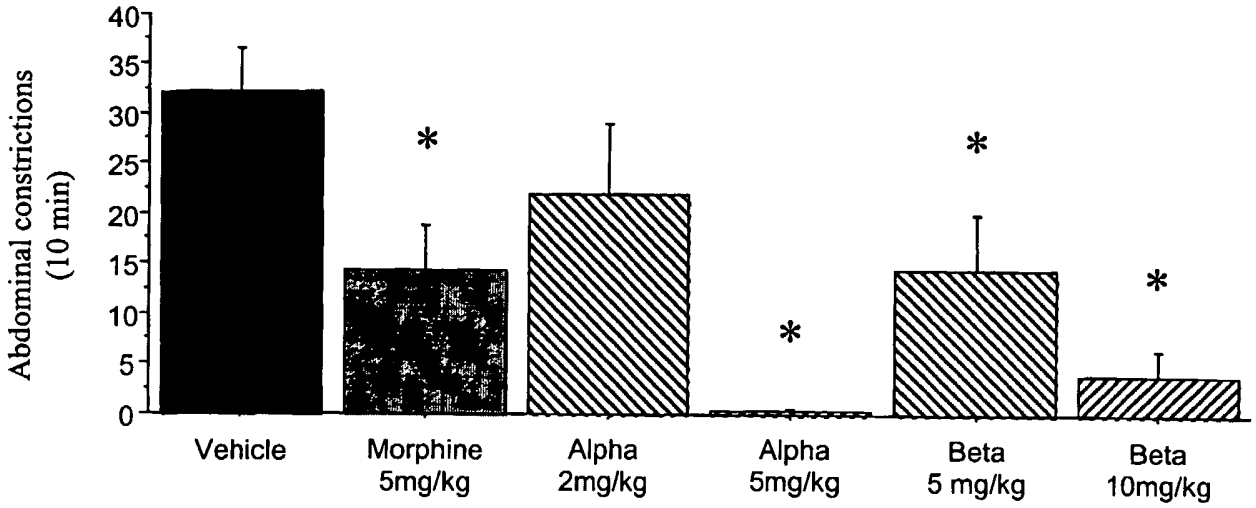


FIGURE 2



*p<0.01 versus vehicle

FIGURE 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/009574

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 2003/130297 A1 (KAO HUAI-HUNG ET AL) 10 July 2003 (2003-07-10) cited in the application the whole document	1-8
A	US 2003/157167 A1 (KAO HUAI-HUNG ET AL) 21 August 2003 (2003-08-21) the whole document	1-8

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 2005	13/09/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx 31 651 epo nl, Fax: (+31–70) 340–3016	Trauner, H-G

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Information on patent family members

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PCT/US2005/009574

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Information on patent family members

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