# METHOD OF THERAPEUTIC ADMINISTRATION OF DHE TO ENABLE RAPID RELIEF OF MIGRAINE WHILE MINIMIZING SIDE EFFECT PROFILE

## TECHNICAL FIELD OF THE INVENTION

**[0001]** The present invention relates to methods for treatment of migraine. In particular, the present invention relates to methods for treatment of migraine and related symptoms while minimizing side-effects, or adverse effects, associated with administration of medications that alleviate migraine symptoms. More specifically, the invention relates to pharmaceutical compositions containing dihydroergotamine (DHE) and methods in which these pharmaceutical compositions are administered to patients for the treatment of migraine headaches without side effects.

## BACKGROUND OF THE INVENTION

**[0002]** Migraine is the most common headache causing patients to consult a physician. According to the American Migraine Study II, approximately 28 million people in the United States aged 12 and older (approximately 13 percent of the population) suffer from headaches that fit the medical definition of migraine established by the International Headache Society. This corresponds to one migraine sufferer in every four U.S. households. The percentage of patients whose headaches fit the medical definition of migraine who are being diagnosed has increased compared to a decade ago. A majority of all migraine sufferers (53 percent) characterize their pain as causing either severe impairment or forcing them to retreat to their beds sometimes for days at a time. There have been no dramatic changes in the way physicians approach the treatment of migraine in the past 10 years. (Lipton RB et al., Headache, (2001) 41:638-645, 646-657)

**[0003]** A three-item Identification of Migraine (ID Migraine) clinical decision rule for the diagnosis of migraine has been developed. (Stewart WF et al., Neurology 1994;44(6 suppl 4):S17-23.) A migraine is a type of primary headache that some people get repeatedly over time. Migraines are different from other headaches because they occur with symptoms such as nausea, vomiting, or sensitivity to light. In most people, a throbbing pain is felt only on one side of the head. Migraines are classified as either "with aura" or "without aura." An aura is a group of

neurological symptoms, usually vision disturbances that serve as warning sign. Patients who get auras typically see a flash of brightly colored or blinking lights shortly before the headache pain begins. However, most people with migraines do not have such warning signs.

**[0004]** Multiple humoral agents have been postulated as being the major factor in migraine. These include serotonin, histamine, prostaglandins, platelet factors, endorphins, and vasoactive neuropeptides. The etiology of migraine has been studied by many investigators. Present research no longer fully supports the vasodilator/vasoconstrictor mechanism of vascular headache, i.e., arterial dilation causes pain and constriction equals relief. Research also has now implicated a sterile inflammation, possibly occurring in the *dura mater*, as the causative factor for vascular head pain. An unknown trigger activates perivascular trigeminal axons, which release vasoactive neuropeptides (substance P, calcitonin gene-related peptide, etc.). These agents produce the local inflammation i.e., vasodilation, plasma extravasation, mast cell degranulation which cause transmission of impulses to the brain stem and higher centers which in turn register as head pain (Moskowitz, M.A. (1992) Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. *Trends Pharmacol. Sci.* 13, 307–311).

**[0005]** Migraine therapy is either prophylactic or symptomatic. Prophylactic medication may be selected for a patient having two to four or more headaches per month, if they are severe enough to interfere with daily activities. Beta blockers such as propranolol (INDERAL®) are the most commonly used. Other medications frequently used include serotonin antagonists such as methysergide maleate (SANSERT®), calcium channel blockers (VERAPAMIL®), amytryptyline (ELAVIL®), and ergotamine preparations with belladona alkaloids and phenobarbital. All of these medications have significant side effects including sedation, loss of energy and drive, dry mouth, constipation, weight gain, and gastrointestinal cramping and distress. For symptomatic treatment, ergotamine with caffeine (CAFERGOT®) is commonly used. Other medications employed for treating migraine include isometheptene mucate (MIDRIN®), non-steroidal anti-inflammatory drugs (NSAID's such as MOTRIN®, NAPROXEN®, etc.), dihydroergotamine and the newer triptans, such as sumatriptan (IMITREX®), etc. When narcotics, such as FIORINAL WITH CODEINE® (butalbital with codeine) are used frequently, additional hazards, including the considerable potential for rebound headaches and habituation are encountered.

**[0006]** The administration of serotonin agonists is well established for the treatment of migraine headache. The serotonin agonists most widely used are the triptans, including

sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, frovatriptan and almotriptan. These compounds bind specifically to serotonin 5-$HT_{1D/1B}$ receptors. To a lesser degree, ergot alkaloids such as ergotamine tartrate (referred to herein as ergotamine) and dihydroergotamine mesylate (also referred to as dihydroergotamine or DHE) are also used to a variety of disease states, including, but not limited to the treatment of acute migraine.

**[0007]** Ergotamine and DHE have very low rectal, oral, sublingual and intranasal bioavailability (only 2% to 10% of the administered dose reaches the systemic circulation). These administration routes also result in relatively slow onset of therapeutic efficacy, ranging from 45 minutes for intranasal to 2 hours for oral or sublingual delivery. IV administration has high bioavailability and onset of therapeutic efficacy, usually much less than 30 minutes. However, injections are painful, cause local inflammation, reduce compliance, and because administration by IV requires costly clinical supervision, it would be very desirable to administer the ergot alkaloids by pulmonary inhalation. Pulmonary inhalation of the ergot alkaloids would minimize metabolism before the drugs can reach the circulation because there is rapid transport from the alveolar epithelium into the capillary circulation and because of the relative absence of mechanisms for metabolism in the lungs. Pulmonary delivery has been demonstrated to result in up to 92% bioavailability in the case of ergotamine tartrate. Pulmonary inhalation administration would also avoid gastrointestinal intolerance typical of migraine medications and minimize the undesirable taste experienced with nasal and sublingual administration due to the bitterness of the ergot alkaloids. Pulmonary inhalation would minimize the reluctance to administer treatment associated with the invasiveness of injection and the cost of clinical supervision. Pulmonary inhalation also would allow for rapid relief from the migraine symptoms, as it would deliver the drug to the systemic circulation as fast as an IV bolus, less than 30 minutes, without the invasive nature of injection.

**[0008]** Dihydroergotamine (DHE) was identified as an effective treatment for migraine nearly fifty years ago (Raskin, Neurology 36:995 997 (1986); Silberstein, et al., Headache 30:334 339 (1990); Saadah, Headache 32:18 20 (1992); and Winner, Headache 33:471 475 (1993)). Despite numerous references describing aerosol delivery of ergotamine tartrate, also referred to as ergotamine, for pulmonary inhalation, there are few, if any, teachings related to the delivery of DHE via pulmonary inhalation. Delivery of DHE in the same manner as ergotamine tartrate is not easily accomplished because DHE is very difficult to stabilize in any of the above

formulations. DHE (D.H.E. 45®-Novartis) has been administered by intramuscular or intravenous (IV) injection for over 50 years (Belgrade, et al., Neurology 39:590 592 (1989); Winner, Headache 33:471 475 (1993)). DHE (MIGRANAL®- Novartis) has been administered by nasal administration for 10 years. DHE is also effective when given subcutaneously (Klapper, et al., Headache 32:21 23 (1992); Winner, et al., Arch. Neurol. 53:180 184 (1996); and Becker, et al., Headache 36:144 148 (1996)). However, its administration has been associated with an undesirable side effect profile: nausea, emesis, chest tightness and related cardiovascular effects such as blood pressure instability and arterial constriction, have been reported with its use.

**[0009]** Although effective in the treatment of migraine, DHE administration is often accompanied by side effects such as nausea, vomiting and chest pain (Winner, et al., Arch. Neurol. 53:180 184 (1996)). Other side effects observed from postmarketing experience in patients receiving D.H.E. 45® (dihydroergotamine mesylate) injection, USP, include vasospasm, paraesthesia, hypertension, dizziness, anxiety, dyspnea, headache, flushing, diarrhea, rash, increased sweating, cardiac valvulopathy, and pleural and retroperitoneal fibrosis seen after long-term use of dihydroergotamine. At least one side effect, nausea, occurs more frequently after intravenous administration than after intramuscular or intranasal administration. When given subcutaneously at a concentration of only 1.5 mM, DHE has been reported to cause nausea in nearly 16% of treated patients (Winner, et al., Arch. Neurol. 53: 80 184 (1996)). The currently accepted treatment algorithms for injection or IV use of DHE (see Figure 6) call for the administration of an antiemetic prior to or concurrent with administration of DHE to prevent nausea. Patients with known cardiovascular disease are not qualified to receive DHE treatment.

**[0010]** Notwithstanding these undesirable side effects DHE is still considered the "gold standard" for treatment of severe migraine, cluster headache, chronic daily headache. DHE has a longer duration of action than sumatriptan, so headache recurrence rates are lower with its use. (Winner P, et al. A double blind study of subcutaneous dihydroergotamine versus subcutaneous sumatriptan in the treatment of acute migraine. Arch Neurol (1996) 53:180-184.) Thus, there exists a need for procedures to deliver therapeutically effective amounts of DHE in a time-sensitive manner, without precipitating the side-effects traditionally associated with its administration.

## SUMMARY OF THE INVENTION

**[0011]** The invention relates to a method for rapid treatment of a disease or condition in an individual with a compound that (a) binds to one or more first receptors, wherein binding of the compound to the first receptors alleviates the disease or condition, and (b) binds to one or more second receptors, wherein binding of the compound to the second receptors causes a side effect, the method comprising: administering to the individual an amount of the compound at a rate sufficient to develop a circulating plasma concentration level of the compound such that compound acts as an agonist against the first receptor and provides relief from the disease or condition, wherein the circulating plasma concentration level of the compound remains below a level necessary for binding to the second receptor to cause a side effect.

**[0012]** In one embodiment, the invention relates to a method for rapid treatment of migraine with DHE, while minimizing side effects, the method comprising: dampening the peak plasma concentration ($C_{max}$) and slightly delaying the peak such as to avoid saturating the dopaminergic and adrenergic receptors, while achieving sufficient binding to the serotonin receptors to alleviate migraine symptoms within a timeframe that permits rapid resolution of migraine symptoms.

**[0013]** In one embodiment, the invention relates to a method for administering DHE or salts, hydrates, polymorphs, prodrugs, ion pairs and metabolites thereof, to a patient in need thereof, an amount of DHE sufficient to reduce a migraine symptom within a 2 hour period, without inducing side-effects.

**[0014]** The invention relates to methods for providing an amount of DHE to an individual sufficient to develop a circulating plasma concentration level of DHE effective for DHE to act as an agonist against a serotonin receptor related to alleviating a migraine symptoms, while insufficient for active binding to an adrenergic or dopaminergic receptor related to nausea and other side effects.

**[0015]** In some embodiments, DHE displays reduced (<50%) or absence of (<20%) active binding at dopaminergic receptors such as $D_2$. In some embodiments, DHE displays absence of (<20%) active binding at 5-$HT_3$ receptors. In some embodiments, In some embodiments, DHE displays reduced (<60%) or absence of (<20%) active binding at adrenergic receptors.

**[0016]** In one embodiment, the DHE is administered by any method at a rate such that the $C_{max}$ is less than 40,000 pg/ml concentration in the circulating plasma in humans, and the time following administration when the peak plasma concentration is attained ($T_{max}$) occurs within 30 minutes after administration.

**[0017]** In some embodiments, $C_{max}$ of DHE is less than 20,000 pg/mL, or less than 15,000 pg/mL, or less than 10,000 pg/mL, or less than 7,500 pg/mL in the circulating plasma. In some embodiments, $T_{max}$ of DHE is preferably less than 20 minutes, and most preferably 15 minutes in the circulating plasma.

**[0018]** According to one aspect of the invention the $C_{max}$ of DHE administered by a method of the invention is at least 5-fold, 10-fold or 15-fold reduced from the $C_{max}$ of DHE administered by direct or slow bolus intravenous delivery.

**[0019]** According to one aspect of the invention the $T_{max}$ of DHE administered by a method of the invention is at least 1 minute delayed from the $T_{max}$ of DHE administered by direct intravenous delivery, and the AUC (or area of the curve of the concentration of the drug in the systemic circulation versus time) of the drug delivered by the method of the invention is within 75% of the comparable IV delivered dose.

**[0020]** According to one aspect of the invention the DHE formulation is administered to an individual by a breath activated metered dose inhaler, wherein the DHE is administered at a rate such that the peak plasma concentration ($C_{max}$) is less than 10,000 pg/ml concentration in the circulating plasma in humans, and the time ($T_{max}$) following administration when the peak plasma concentration is attained, is less than 20 minutes after administration, and further wherein the DHE formulation is administered without administering an anti-emetic to the individual.

**[0021]** According to the methods of the invention, administration of DHE to achieve $C_{max}$ and $T_{max}$ as described above, results in at least partial relief from a migraine syndrome including but not limited to pain, nausea, phonophobia and photophobia, within 30 minutes and sustained relief for 24 hours, but does not result in drug induced nausea, cardiovascular side effects or other adverse effects.

**[0022]** According to one embodiment, the at least partial relief from a migraine syndrome is measured by a drop from a IHS score of greater than "0" for a migraine symptom at the time of administration of DHE, to a score of $\leq 1$ at 30, 60, 90 or 120 minutes following administration.

**[0023]** According to the methods of the invention, administration results in peak plasma concentrations of the primary active metabolites, including but not limited to 8-hydroxy dihydroergotamine, at less than 40,000 pg/ml at Cmax. In some embodiments, $C_{max}$ of the primary metabolites is preferably less than 1,000 pg/mL, more preferably less than 500 pg/mL, and most preferably less than 200 pg/mL in the circulating plasma. In some embodiments, the $T_{max}$ of the primary metabolites is preferably less than 90 minutes, and most preferably 60 minutes in the circulating plasma..

**[0024]** In one aspect of the invention, the method involves administration to the systemic circulation of an unit dose of less than 3.0 mg DHE or salts, hydrates, polymorphs prodrugs, ion pairs and metabolites thereof. In a preferred embodiment, an unit dose of 1.0 mg is administered.

**[0025]** The invention also relates to suitable DHE formulations that achieve the desired delivery profile when administered to an individual.

**[0026]** According to the methods of the invention a DHE formulation may be administered by any mode, including but not limited to, intravenous, intra-arterial, intraperitoneal, intrapulmonary, oral, sublingual, buccal, intranasal, oral inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, iontophoresis, transdermal, intraocular, intrathecal, transmucosal, and transdermal delivery.

**[0027]** In a preferred mode, the method of administration is by pulmonary inhalation using aerosols, dry powder inhalers, nebulizers, vaporizers, pressurized metered dose inhalers (pMDIs) and the like. In a more preferred embodiment a pMDI such as a breath activated metered dose inhaler (for example, TEMPO™ Inhaler from Map Pharmaceuticals, Mountain View, California) is used to administer DHE.

**[0028]** The invention also relates to kits comprising DHE formulations and instructions for use thereof. In a preferred embodiment, an inhaler device is included. In one embodiment of this kit, the inhaler device is loaded with a DHE formulation. In another embodiment the kit comprises one or more unit doses of the DHE formulation. In one embodiment, the inhaler device is a pMDI such as a breath activated metered dose inhaler (TEMPO™ Inhaler).

**[0029]** The invention further relates to an inhaler device comprising one or more unit doses of a DHE formulation wherein each unit dose is administered at a rate such that the peak plasma concentration ($C_{max}$) is less than 10,000 pg/ml concentration in the circulating plasma in humans, and the time ($T_{max}$) following administration when the peak plasma concentration is attained, is less than 30 minutes after administration.

**[0030]** The present invention and other objects, features, and advantages of the present invention will become further apparent in the following Detailed Description of the Invention and the accompanying Figures and embodiments.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0031]** FIG. 1 shows percentage of subjects obtaining relief from pain with DHE versus placebo.

**[0032]** FIG. 2 shows pharmacokinetic profiles for achieving pain relief with minimal side effects.

**[0033]** FIG. 3 shows radioligand receptor binding profile for serotonergic receptor subtypes based on dose and administration route. Less than 20% was classed as inactive binding. "(h)" represents cloned human receptor subtypes.

**[0034]** FIG. 4 shows radioligand receptor binding profile for adrenergic and dopaminergic receptor subtypes based on dose and administration route. Less than 20% was classed as inactive binding. "(h)" represents cloned human receptor subtypes and "NS" indicates non-specific binding.

**[0035]** FIG. 5 shows selective agonism at 5-$HT_{1B}$ and 5-$HT_{2B}$ receptors at various concentrations of DHE.

**[0036]** FIG. 6 shows currently accepted treatment algorithms for injection or IV administration of DHE.

**[0037]** FIG. 7 shows geometric mean 8'OH-DHE concentrations over time following administration of DHE by inhalation and intravenous (IV) routes.

## DETAILED DESCRIPTION OF THE INVENTION

**[0038]** Use of the term Dihydroergotamine (DHE) according to the methods of invention comprises DHE or salts, hydrates, polymorphs prodrugs, ion pairs and metabolites thereof.

**[0039]** The invention relates to a method for administering DHE or salts, hydrates, polymorphs prodrugs, ion pairs and metabolites thereof, to a patient in need thereof, an amount of DHE sufficient to reduce a migraine symptom within a specified period hour period, without inducing side-effects.

**[0040]** To reduce a migraine symptom within a specified period hour period may involve providing partial relief from at least one migraine syndrome which includes but is not limited to pain, nausea, phonophobia and photophobia, within a period 30, 60, 90, 120 or 180 minutes. Reduction of a migraine symptom further may comprise providing sustained relief for 6, 12, 18, 24 or 36 hours.

**[0041]** Relief from any of the migraine symptoms is measured by a drop from a IHS score of greater than "0" (score of >1 for pain) at the time of administration of DHE, to a score of $\leq 1$ at 30, 60, 90, 120 or 180 minutes following administration. However, freedom from pain (or other severe symptoms) require a reduction in grading of that symptom from an initial >0 result (score of >1 for pain) to 0 at the time point in question.

**[0042]** To reduce a migraine symptom without inducing side-effects may involve administration of therapeutically effective amounts of DHE not resulting in drug induced nausea, emesis, chest tightness and related cardiovascular effects such as blood pressure instability and arterial constriction, or any other adverse effects known to be associated with treatment of migraine with DHE.

**[0043]** The invention relates to methods for providing an amount of DHE to an individual sufficient to develop a circulating plasma concentration level of DHE effective for DHE to act as an agonist against a serotonin receptor related to alleviating a migraine symptoms, wherein the $C_{max}$ is attained within a time period ($T_{max}$) sufficient for providing partial relief from at least one migraine syndrome including but not limited to pain, nausea, phonophobia and photophobia, within a period 30, 60, 90, 120 or 180 minutes, or providing sustained relief for 6, 12, 18, 24 or 36 hours.

**[0044]** Further, the $C_{max}$ attained within a time period ($T_{max}$) according to administration methods of this invention are insufficient for active binding of DHE to an adrenergic or dopaminergic receptor and causing nausea and other side effects.

**[0045]** When binding of DHE to an adrenergic or dopaminergic receptor is insufficient for causing nausea and other side effects, DHE displays reduced (less than 50%) or absence of (20% or less) binding at dopaminergic receptors such as $D_2$; and DHE displays reduced (less than 60%) or absence of (20% or less) binding at adrenergic receptors.

**[0046]** According to the invention, DHE is administered by any method at a rate such that the $C_{max}$ is less than 5,000, 10,000, 20,000, 30,000, 40,000, 50,000, or 60,000 pg/ml concentration in the circulating plasma in humans, and the time following administration when the peak plasma concentration is attained ($T_{max}$) occurs within 10, 15, 20, 30, 45 or 60 minutes after administration.

**[0047]** According to the methods of the invention, administration results in peak plasma concentrations of the primary active metabolites, including but not limited to 8-hydroxy dihydroergotamine, at less than 5,000, 10,000, 20,000, 30,000, 40,000, 50,000, 60,000, 100,000 or 200,000 pg/ml at $C_{max}$. The $T_{max}$ of the primary metabolites is less than 30, 45, 60, 90, or 120 minutes after administration.

**[0048]** According to one aspect of the invention the $C_{max}$ of DHE administered by a method of the invention is at least 5-fold, 10-fold, or 15-fold reduced from the $C_{max}$ of DHE administered by direct intravenous delivery.

**[0049]** According to one aspect of the invention the $T_{max}$ of DHE administered by a method of the invention is at least 1, 2, 5, 10 or 15 minutes delayed from the $T_{max}$ of DHE administered by direct intravenous delivery, and the AUC (or area the curve of the concentration of the drug in the systemic circulation versus time) of the drug delivered by the method of the invention is within 75% of the comparable IV delivered dose.

**[0050]** In one aspect of the invention, the method involves administration of an unit dose comprising about 0.5, 1.0, 2.0, 3.0 or 5.0 mg DHE or salts, hydrates, polymorphs prodrugs, ion pairs and metabolites thereof.

**[0051]** The invention relates to packaged vials, canisters, ampoules, packs, or patches comprising one or more unit doses of DHE. Unit doses may be formulated and packaged in a

manner suitable for administration by intravenous, intra-arterial, intraperitoneal, intrapulmonary, oral, sublingual, buccal, intranasal, oral inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, iontophoretic, transdermal delivery. In preferred embodiments, the doses of DHE are packaged in a manner suitable for intravenous delivery or pulmonary inhalation.

**[0052]** The invention also relates to suitable solid, liquid or aerosol formulations of DHE that, when administered to a mammal under appropriate conditions, achieve the desired delivery profile defined by AUC, $C_{max}$ and $T_{max}$ values listed above.

**[0053]** According to the methods of the invention a DHE formulation may be administered by any mode necessary to achieve the desired delivery profile defined by $C_{max}$ and $T_{max}$ values listed above, including but not limited to, by intravenous, intra-arterial, intraperitoneal, intrapulmonary, oral, sublingual, buccal, intranasal, oral inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, iontophoretic, transdermal administration.

**[0054]** Typically, the DHE formulation will be distributed, either to clinics, to physicians or to patients, in an administration kit, and the invention provides such a migraine treatment kit. Such kits comprise one or more of an administration device (e.g., syringes and needles, inhalators, etc) and a plurality of unit dosages or a reservoir or cache configured to deliver multiple unit doses of the composition as described above. In one embodiment, the administration device is loaded with a DHE formulation The kit can additionally comprise a carrier or diluent, a case, and instructions for employing the appropriate administration device. In some embodiments, an inhaler device is included. In one embodiment of this kit, the inhaler device is loaded with a reservoir containing the DHE formulation. In another embodiment the kit comprises one or more unit doses of the DHE formulation. In one embodiment, the inhaler device is a pMDI such as a breath activated metered dose inhaler (TEMPO™ Inhaler).

**Dihydroergotamine (DHE) for Treatment of Migraine**

**[0055]** Dihydroergotamine (DHE) is a semi-synthetic ergot alkaloid, which has been used in the treatment of migraine since 1946. Due to structural similarities with physiological molecules, DHE has wide ranging pharmacology (Table 1), mediated by effects on biogenic amine receptors -- specifically serotonin (5-HT) subtypes, adrenergic (α and β) subtypes and dopaminergic (D) subtypes).

**[0056]** Dihydroergotamine is used extensively to treat cluster migraine, pediatric migraine, status migranosis and chronic daily headache, formerly referred to as "transformed" migraine. DHE is currently administered orally and intranasally (MIGRANAL®- Novartis, US5942251, EP0865789A3, and BE1006872A). However, DHE is most often administered by intramuscular/subcutaneous injection or by intravenous injection (D.H.E. 45®-Novartis) in a clinical setting. (Raskin NH, Neurol Clin. 1990 Nov; 8(4):857-65.)

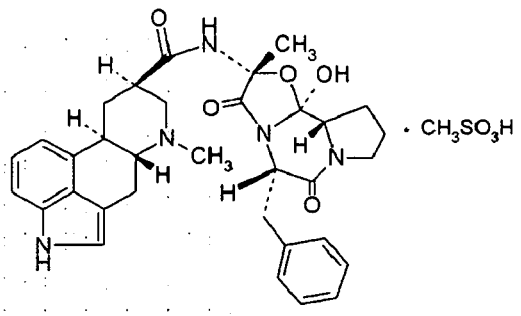
**[0057]** Dihydroergotamine binds with high affinity to 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors. It also binds with high affinity to serotonin 5-$HT_{1A}$, 5-$HT_{2A}$, and 5-$HT_{2C}$ receptors, noradrenaline $\alpha_{2A}$, $\alpha_{2B}$ and $\alpha_1$ receptors, and dopamine $D_{2L}$ and $D_3$ receptors.

**[0058]** The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-$HT_{1D}$ receptors. Two current theories have been proposed to explain the efficacy of 5-$HT_{1D}$ receptor agonists in migraine. One theory suggests that activation of 5-$HT_{1D}$ receptors located on intracranial blood vessels, including those on arteriovenous anastomoses, leads to vasoconstriction, which correlates with the relief of migraine headache. The alternative hypothesis suggests that activation of 5-$HT_{1D}$ receptors on sensory nerve endings of the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release. In addition, dihydroergotamine possesses oxytocic properties.

**[0059]** The ergot alkaloids are less selective than the triptans when binding to 5-$HT_{1D}$, 5-$HT_{1A}$, 5-$HT_{2A}$, 5-$HT_{2C}$, noradrenaline $\alpha_{2A}$, $\alpha_{2B}$, and $\alpha$, dopamine $D_{2L}$ and $D_3$ receptors. In acute migraine therapy, DHE is thought to mediate its effects through 5-$HT_{1B}$ receptors (constriction of intracranial extra-cerebral blood vessels) and 5-$HT_{1D}$ receptors (inhibition of trigeminal neurotransmission).

**[0060]** DHE is known to bind specifically to receptors as shown in Table 1. Table 1 shows affinities of DHE (measured as $IC_{50}$) for specific biogenic amine receptors. Potent activity at 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors and wide ranging receptor-binding activity is observed for DHE. (Silberstein, S.D., McCrory, D.C. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. Headache (2003) 43:144-166.)

**[0061]** The chemical structure of DHE is shown below:



$C_{34}H_{41}O_8N_5S$

| Serotonin Receptor Subtype | Affinity $IC_{50}$ (nM) | Adrenergic Receptor Subtype | Affinity $IC_{50}$ (nM) | Dopaminergic Receptor Subtype | Affinity $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| 1A | 0.4 | α1a | 6.6 | D2 | 1.2 |
| 1B | 0.7 | α1b | 8.3 | D3 | 6.4 |
| 1D | 0.5 | α2a | 1.9 | D4 | 8.7 |
| 1E | 1100 | α2b | 3.3 | | |
| 1F | 180 | α2c | 1.4 | | |
| 2A | 9 | | | | |
| 2C | 1.3 | β1 | 3100 | | |
| 3 | 3700 | β2 | 2700 | | |
| 5 | 60 | β3 | 271 | | |

***Table 1:*** *Receptor binding activity of Dihydroergotamine mesylate (DHE)*

**Formulations and Dosage Forms**

**[0062]** A number of studies have been conducted in adults to demonstrate the efficacy and safety of intravenous DHE. The current method of administering intravenous DHE by using repeated intravenous doses of DHE to treat severe migraines was introduced by Raskin. (Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. Neurology 1986; 36: 995-997). References to "direct intravenous delivery" in the specification is understood to refer to direct IV administration of DHE according to the procedure set forth in Raskin (Neurology 36: 995-997 (1986)).

**[0063]** Recently, formulations of DHE by itself and in combination with nonsteroidal analgesics have been developed for intramuscular autoinjectors (US 20030040537, US6077539, WO005781A3, EP1165044A2, CN1347313T, and AU0038825A5). DHE in combination with potent analgesics had also been formulated for treatment by intranasal administration (US5756483, EP0689438A1, AU6428894A1, and WO9422445A3). Spray or aerosol formulations have also been developed for the sublingual administration of DHE (US20030017994). Ergotamine tartrate has been administered by injection, rectally with suppositories and via inhalation with metered dose inhaler (MEDIHALER–ERGOTAMINE®; 3M Health Care, Northridge, California), but is most commonly administered orally or sublingually.

**[0064]** There are numerous recent citations of ergotamine tartrate formulations for administration via inhalation (US6488648, US6451287, US6395300, US6395299, US6390291, US 6315122, US6179118, US6119853, US6406681) and specifically in propellant based metered dose inhaler (MDI) formulations (US5720940, US5683677, US5776434, US5776573, US6153173, US6309624, US6013245, US6200549, US6221339, US6236747, US6251368, US6306369, US6253762, US6149892, US6284287, US5744123, US5916540, US5955439, US5992306, US5849265, US5833950, US5817293, US6143277, US6131566, US5736124, US5696744). In the late 1980s 3M developed, received approval for and marketed a pulmonary inhalation formulation of an ergotamine tartrate (MEDIHALER–ERGOTAMINE®). It was removed from the market in the 1990s due to difficulties with inconsistent formulation.

**[0065]** Powders for inhalation in dry powder inhalation devices using ergotamine tartrate have also been described (US6200293, US6120613, US6183782, US6129905, US6309623, US5619984, US4524769, US5740793, US5875766, US6098619, US6012454, US5972388, US5922306). An aqueous aerosol ergotamine tartrate formulation for pulmonary administration has also been described (US5813597).

**[0066]** The invention is directed to a pharmaceutical composition in unit dose form containing DHE in an amount such that one or more unit doses are effective in the symptomatic treatment of migraine headache when administered to a patient. The composition may contain excipients. In order to retard the rate of oxidative degradation of the composition, one or more antioxidants may be added. Any salt of DHE may be used but the mesylate salt is preferred. In all cases, formulations may be prepared using methods that are standard in the art (see, e.g., Remington:

The Science and Practice of Pharmacy , 21st ed., Lippincott Williams & Wilkins (2005)). In general, patients receive a total dosage of between 0.1 and 10.0 mg, preferably 0.5 to 5.0 mg, or more preferably 1.0 – 2.0 mg per migraine attack. The dose of the DHE formulation administered to an individual (such as human) will vary with the particular composition and the method of administration, such as to achieve the necessary biogenic amine receptor binding profile required for treating migraine without triggering side effects or adverse effects.

**[0067]** The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for an individual, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient. These unit dosage forms can be stored in a suitable packaging in single or multiple unit dosages and may also be further sterilized and sealed.

**[0068]** Also provided are articles of manufacture comprising the compositions described herein in suitable packaging. Suitable packaging for compositions described herein are known in the art, and include, for example, vials (such as sealed vials), canisters with metering valves, vessels, ampoules, bottles, jars, flexible packaging (e.g., sealed Mylar or plastic bags), and the like. These articles of manufacture may further be sterilized and/or sealed.

**[0069]** The compositions may further comprise additional ingredients, for example preservatives, buffers, tonicity agents, antioxidants and stabilizers, nonionic wetting or clarifying agents, viscosity-increasing agents, absorption enhancing agents, and the like.

**[0070]** Suitable absorption enhancement agents include N-acetylcysteine, polyethylene glycols, caffeine, cyclodextrin, glycerol, alkyl saccharides, lipids, lecithin, dimethylsulfoxide, and the like.

**[0071]** Suitable preservatives for use in a solution include polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, disodium edetate, sorbic acid, benzethonium chloride, and the like. Typically (but not necessarily) such preservatives are employed at a level of from 0.001% to 1.0% by weight.

**[0072]** Suitable buffers include boric acid, sodium and potassium bicarbonate, sodium and potassium borates, sodium and potassium carbonate, sodium acetate, sodium biphosphate and the like, in amounts sufficient to maintain the pH at between about pH 6 and pH 8, and preferably, between about pH 7 and pH 7.5.

[0073] Suitable tonicity agents are dextran 40, dextran 70, dextrose, glycerin, potassium chloride, propylene glycol, sodium chloride, and the like, such that the sodium chloride equivalent of the ophthalmic solution is in the range 0.9 plus or minus 0.2%.

[0074] Suitable antioxidants and stabilizers include sodium bisulfite, sodium metabisulfite, sodium thiosulfite, thiourea, caffeine, chromoglycate salts, cyclodextrins and the like. Suitable wetting and clarifying agents include polysorbate 80, polysorbate 20, poloxamer 282 and tyloxapol. Suitable viscosity-increasing agents include dextran 40, dextran 70, gelatin, glycerin, hydroxyethylcellulose, hydroxmethylpropylcellulose, lanolin, methylcellulose, petrolatum, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose and the like.

**Modes of administration**

[0075] The compositions described herein can be administered to an individual (such as human) via various routes, including, for example, intravenous, intra-arterial, intraperitoneal, intrapulmonary, oral, inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, intraocular, intrathecal, transmucosal, and transdermal. In one embodiment of the invention, nanoparticles (including protein or carbohydrate nanoparticles, co-formulated with drug) of the inventive compounds can be administered by any acceptable route including, but not limited to, orally, intramuscularly, transdermally, intravenously, through an inhaler or other air borne delivery systems and the like.

[0076] When preparing the composition for injection, particularly for intravenous delivery, the continuous phase preferably comprises an aqueous solution of tonicity modifiers, buffered to a pH range of about 4 to about 8.5. The pH may also be below 7 or below 6. In some embodiments, the pH of the composition is no less than about 6, including for example no less than about any of 6.5, 7, or 8 (such as about 7.5 or 8).

[0077] In a preferred embodiment the DHE is delivered using inhalation therapy. Many preclinical and clinical studies with inhaled compounds have demonstrated that efficacy can be achieved both within the lungs and systemically. Moreover, there are many advantages associated with pulmonary delivery including rapid onset, the convenience of patient self-administration, the potential for reduced drug side-effects, ease of delivery by inhalation, the elimination of needles, and the like.

**[0078]** Inhalation aerosols from dry powder inhalers, nebulizers, vaporizers and pressurized metered dose inhalers typically include excipients or solvents to increase stability or deliverability of these drugs in an aerosol form. Additionally, the particle size of the drug aerosols may be controlled to provide the uptake characteristics consistent with the methods of the invention. Typically, particle sizes are controlled to desirable sizes known by those skilled in the art. For example, when using dry powder inhalers (DPI's), the drug particles are generated from the bulk drug by attrition processes such as grinding, micronizing, milling, or by multiphase precipitation processes such as spray drying, solution precipitation, , supercritical extraction/precipitation or lyophilization to yield powders that can be dispersed in the propellant to obtain an acceptable particle size for delivery to the lungs. As dry powder formulations are prone to aggregation and low flowability which can result in diminished efficiency, scrupulous attention is required during milling, blending, powder flow, filling and even administration to ensure that the dry powder aerosols are reliably delivered and have the proper particle size distribution for delivery to the lungs.

**[0079]** Nebulizers generate an aerosol from a liquid, some by breakup of a liquid jet and some by ultrasonic vibration of the liquid with or without a nozzle. Liquid formulations are prepared and stored under aseptic or sterile conditions since they can harbor microorganisms. The use of preservatives and unit dose packaging is contemplated. Additionally solvents, detergents and other agents are used to stabilize the drug formulation.

**[0080]** Pressurized metered dose inhalers, or pMDIs, are an additional class of aerosol dispensing devices. pMDIs package the compound in a canister under pressure with a solvent and propellant mixture, usually chlorofluorocarbons (CFCs,), or hydroflouroalkanes (HFAs). Upon being dispensed a jet of the mixture is ejected through a valve and nozzle and the propellant "flashes off" leaving an aerosol of the compound. Due to the high speed ejection of the aerosol from the nozzle, some of the drug may impact ballistically on the tongue, mouth and throat and never reach the lung.

**[0081]** While aerosol delivery of ergotamine tartrate for pulmonary inhalation is widely known, delivery of DHE via pulmonary inhalation has been used rarely, as DHE is very difficult to stabilize in formulations suitable for pulmonary delivery. To maintain potency and activity the DHE must be formulated in a solution, powder or suspension that can be stabilized without excipients or with excipients that are not toxic to the lungs. Since DHE is extremely sensitive

and will degrade on exposure to light, oxygen, heat and in the presence of many chemical compounds commonly used in medicinal formulations, stabilization is not easily achieved. The current formulations for delivery of DHE by aqueous nasal sprays or by injection require chelating or complexing agents, such as dextran or cyclodextrins, to stabilize the DHE in solution. To preserve the DHE solution from degradation it is sealed in difficult-to-use dark-glass vials that must be opened with a complicated opener and transferred to injector or spray applicator immediately prior to use. Only recently stable formulations for pulmonary delivery of DHE have been described in US App. Ser. No. 10/572,012 and WO2005/025506A2.

**[0082]** WO2005/025506A2 describes suitable, stable formulations of dihydroergotamine, or pharmaceutically acceptable salts thereof, to administer dry powders and propellant suspensions via pulmonary aerosol inhalation or nasal spray inhalation. In one embodiment, DHE is used as the mesylate salt. The DHE powder is generated using supercritical fluid processes which offer significant advantages in the production of DHE particles for inhalation delivery and produce respirable particles of the desired size in a single step. The disclosures of US App. Ser. No. 10/572,012 and WO2005/025506A2 are incorporated herein by reference in their entirety.

**[0083]** In a preferred embodiment, the inhaled dosing is carried out with a breath actuated inhaler such as the Tempo™ Inhaler (Map Pharmaceuticals, Inc., Mountain View, California). The Tempo™ Inhaler is a pressurized metered-dose inhaler (pMDI) which addresses limitations of standard pMDI inhalers: inconsistent dosing and drug delivery inefficiency. The Tempo Inhaler provides breath actuation, enhancing patient compliance, and efficient, reliable dose-to-dose consistency that is independent of the inhalation flow rate. It achieves these advantages by combining proprietary features such as the breath synchronized trigger and the flow control chamber and dose counter/lockout in a small, easy to use device. These advanced aerodynamic control elements are driven only by the patient's breath, avoiding expensive, power consuming electronics, resulting in an affordable, reliable and disposable platform.

**Measuring Efficiency of DHE Administration**

**[0084]** The current invention teaches a method of administration of DHE that minimizes or eliminates side effects while at the same time achieving a dosing profile sufficient to provide effective and rapid relief from the four primary symptoms of migraine syndrome: pain, nausea, phonophobia and photophobia. In clinical trials conducted by the inventors, an unanticipated

phenomenon was observed. When DHE was administered in the aforementioned manner, a very high "spike" in peak plasma concentration was unexpectedly avoided, the side effects of nausea, chest tightness or pain, blood pressure excursions, emesis could be minimized or completely eliminated while still achieving rapid relief from the migraine symptoms.

**[0085]** Efficacy of a migraine therapy regimen can be evaluated based on primary and secondary endpoints. Primary efficacy endpoint may be a pain-free response rate at about 2 hours post-dose. Secondary efficacy endpoints examine 3 areas of interest: pain-free response at time points earlier than 2 hours post-dose; non-progression of headache; and impact on normal activities.

**[0086]** All four migraine symptoms -- pain, nausea, phonophobia and photophobia -- are scored at each time point on a four point scale developed by the International Headache Society (IHS; International Headache Society Committee on Clinical Trials in Migraine. Guidelines for controlled clinical trials of drugs in migraine, 1st ed. Cephalalgia 1991; 11:1-12):

0 = none
1 = mild symptom, not interfering with normal daily activities
2 = moderate symptom, causing some restriction to normal activities
3 = severe, leading to inability to perform normal daily activities

**[0087]** Headache pain intensity is measured on the 4-point severity scale (0=no pain, 1=mild, 2=moderate, 3=severe). The average time to headache improvement (one point below the original intensity), to mild headache, and to no headache is measured. An effective migraine therapy would reduce a headache symptom to mild or non by 1.5 to 2 hours.

**[0088]** Relief from any of the four symptoms require a drop from a score of >0 at time of report of onset of migraine attack (score of >1 for pain), to a score of $\leq 1$ at the time point in question. However, freedom from pain (or other symptom) require a reduction in grading of that symptom from an initial >0 result (score of >1 for pain) to 0 at the timepoint in question.

**[0089]** Functional disability (ability to perform usual daily activities) is measured with a 4 point scale:

0 = not at all impaired
1 = slightly impaired
2 = moderately impaired
3 = severely or completely impaired

**[0090]** There is a further question (How well did your Study Medication work?) at certain timepoints asking subjects to evaluate the "global effectiveness" of their study medication using a 7 point categorical scale:

0 = very much better
1 = much better
2 = a little better
3 = no change
4 = a little worse
5 = much worse
6 = very much worse

**Mechanisms of action**

**[0091]** Investigation of receptor binding at the $C_{max}$ concentrations described in detail in Examples 2 and 3, provided a rationale for the differences observed in the adverse effect profile. Without being bound by theory, it is hypothesized that a method for treating migraine with DHE without triggering side effects can be achieved by controlling the $C_{max}$ concentration to minimize binding to dopaminergic and adrenergic receptors and thus avoiding side effects, while achieving sufficient serotonin receptor binding to be effective in treating migraine symptoms.

**[0092]** Clinical data (Table 2) show that inhaled dihydroergotamine reduces incidence of nausea compared to intravenous administration (8% vs. 63% respectively). 5-$HT_3$ receptors are known to be implicated in nausea. Antagonists at these receptors, such as ondansetron and granisetron prevent chemotherapy-induced nausea and vomiting. However, a potential agonist role of DHE at 5-$HT_3$ receptors can be ruled out by inactive binding (<20%) for all DHE delivery routes investigated (Figure 3). Subsequent functional assays also confirmed lack of agonist or antagonist activity at 5-$HT_3$ receptors.

**[0093]** The likely adverse effect profile of DHE is secondary to agonist activity at 5-$HT_{1A}$, 5-$HT_{2A}$, and dopamine $D_2$ receptors. (Silberstein, S.D., McCrory, D.C. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. Headache (2003) 43:144-166.) The similar levels of 5-$HT_{1A}$ receptor binding for all doses and administration routes rules out this receptor as the cause for the differential adverse effect profile, in particular for dizziness. Indeed, 5-$HT_{1A}$ receptors are believed to play a role in DHE-mediated migraine prophylaxis. (Hanoun, N., et al. Dihydroergotamine and its metabolite, 8-hydroxy-dihydroergotamine, as 5-HT1A receptor agonists in the rat brain. British Journal of Pharmacology 2003; 139:424–434.)

**[0094]** DHE has excitatory actions at vascular α-adrenergic receptors and have agonist activity at constrictor 5-$HT_{2A}$ receptors. These actions underlie peripheral vasoconstrictor effects, in particular on coronary artery smooth muscle. As such, DHE and related ergot compounds are contraindicated in coronary and peripheral vascular disease. It is notable however that $C_{max}$ binding activity was lower for the higher inhaled (14%) vs. intravenous dosing (83%) at 5-$HT_{2A}$ receptors. The effect of other serotonergic subtypes and adrenergic types on the adverse effect profile is not certain. However, binding at $C_{max}$ following intravenous administration yields significantly higher binding (Figures 3-5) vs. inhaled $C_{max}$, which may play a role in nausea, in particular for adrenergic blockade.

**[0095]** Both neuronal and vascular mechanisms have been proposed as the basis of actions of 5-HT in migraine. The vasodilatory theory of migraine suggests that extracranial arterial dilation during an attack is related to migraine pain. In the neurogenic dural inflammation theory of migraine, inflammation of the dural membrane surrounding the brain is due to release of neuropeptides from primary sensory nerve terminals. Substance P, calcitonin gene-related peptide and NO all play a role in the dural inflammatory cascade. NO is suspected to play a key role in migraine since NO donors cause a dose-dependent headache with several migrainous characteristics. A cause of migraine could be increased amounts and/or affinity of an enzyme in the NO-triggered cascade of reactions (Olesen *et al.*, Trends Pharmacol. Sci. 1994;15:149–153).

**[0096]** It has been shown that 5-$HT_{2B}$ receptors stimulate the NO production in cell lines (Manivet P., *et al.*, PDZ-dependent activation of nitric-oxide synthases by the serotonin 2B receptor. J. Biol. Chem. 2000;275:9324–9331) and relaxation of the pig cerebral artery (Schmuck *et al.*, Eur. J. Neurosci. 1996;8:959–967). Thus, 5-$HT_{2B}$ receptorss located on endothelial cells of meningeal blood vessels have been proposed to trigger migraine headache through the formation of NO. The long half-life of DHE may account for the low rate of headache recurrence at least partially through permanent inhibition of vascular 5-$HT_{2B}$-dependent second messengers (NO) *via* its major active metabolite 8′-OH-DHE. (Schaerlinger B., et al., British Journal of Pharmacology (2003) 140, 277–284.)

**[0097]** D2 receptor antagonists, i.e. metoclopramide and domperidone, are effective anti-nausea therapies. DHE at IV dose $C_{max}$ levels exhibits 50% receptor binding in D2 assays (Figure 5) and therefore may result in the clinically reported nausea and dizziness, mediated through agonist activity. Conversely, no binding affinity was reported after inhaled dosing. In

addition to data reported here, DHE also has minimal binding activity at muscarinic (M) receptors, and thus rules out chemoreceptor trigger zone M receptor-mediated nausea. (McCarthy, B.G., Peroutka, S.J., Comparative neuropharmacology of dihydroergotamine and sumatriptan (GR 43175). Headache 1989; 29:420-422.)

**[0098]** The receptor-binding studies described in Examples 2 and 3 may explain the unexpected results from the novel method of treating migraine rapidly with DHE, while minimizing side effects. The method dampens the peak plasma concentration ($C_{max}$) and slightly delays the peak so as to avoid saturating the dopaminergic and adrenergic receptors, while achieving sufficient binding to the serotonin receptors to have the desired therapeutic effect of treating migraine.

## EXAMPLES

**[0099]** Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following examples are illustrative only, and not limiting of the remainder of the disclosure in any way whatsoever.

### Example 1: Pharmacokinetic profile of DHE required to achieve pain relief.

**[0100]** Figure 1 shows the rapid pain relief (within 10 minutes) achieved by administering DHE by a method that achieves the two lower peak plasma concentration profiles shown in Figure 2.

**[0101]** Figure 2 shows DHE plasma profiles for 1 mg IV-administered DHE, compared to 6 inhalations (1.22 mg inhaled/fine particle dose), 4 inhalations (0.88 mg inhaled/fine particle dose) and 2 inhalations (0.44 mg inhaled/fine particle dose) of DHE respectively. A large plasma spike was observed following IV DHE administration, but not with inhaled delivery of DHE. This plasma spike difference (of at least "10" fold) was hypothesized to be associated with the reduced side effect profile, despite smaller differences in AUC between 1 mg IV and 0.88 mg inhaled DHE.

**[0102]** Figure 7 shows the plasma profile of the primary metabolite of DHE, 8'-OH Dihydroergotamine, following intravenous and inhalation delivery of DHE. A larger plasma spike in 8'-OH Dihydroergotamine was observed following IV DHE administration, but not with inhaled delivery of DHE. This plasma spike difference also is hypothesized to be associated with

the reduced side effect profile. The inhalable administration results in a peak plasma concentration of 8-hydroxy-dihydroergotamine of less than 1,000 pg/ml, preferably less than 500 pg/mL, more preferably less than 200 pg/mL at $C_{max}$ in the circulating plasma. The inhalable administration also results in the $T_{max}$ of the primary metabolites (e.g., 8'-OH Dihydroergotamine) to be less than 90 minutes in the circulating plasma.

**[0103]** The inventors have discovered that these slightly delayed, lower peak pharmacokinetic profiles are associated with minimized side effects. The side effects elicited by these administration profiles are shown in the Table 2. The two lower curves, 0.88 mg and 0.44 mg DHE in Figure 2, achieved therapeutic efficacy within 30 minutes, but elicited only minor side effects with the 0.88 mg dose, and no side effects were observed with the 0.44 mg dose. The highest curve, 1.0 mg IV DHE – the typical therapeutic regimen practiced in clinics today- resulted in significant side effects including nausea and emesis. The observed lower $C_{max}$ or peak plasma concentration difference which was approximately 10 times lower than IV, was theorized to be associated with the observed differential side effect profile, while the smaller differences in AUC, differences of only "1.2" fold, between 1 mg IV and 0.88 mg inhaled enabled therapeutic efficacy. The delivery profiles shown in Figure 2 were achieved in this instance by inhalation administration, but could also be achieved by infusion pump, nasal, or iontopheric transdermal or other routes or administration, that were tailored to give a similar slight delay in reaching peak plasma concentrations and a similar damping of peak concentrations, while achieving similar AUCs.

| | 1 mg DHE IV, n=16 (%) | 0.88 mg DHE Inhaled, n=12 (%) |
|---|---|---|
| **Nervous System** | | |
| Dizziness | 7 (44) 7r | 1 (8) |
| Paresthesia | 5 (31) 5r | 0 |
| **Gastrointestinal System** | | |
| Nausea | 10 (63) 10r | 1 (8) |
| Vomiting | 2 (13) 2r | 0 |
| **General disorders** | | |
| Feeling hot | 3 (19) 3r | 0 |
| *r = considered by investigator related to study drug* | | |

***Table 2:*** *Side effects associated with the pharmacokinetic profiles in Figure 2*

**Example 2: Receptor binding at the $C_{max}$ concentrations**

**[0104]** A differential adverse effect profile was reported in a clinical study comparing 1 mg IV-administered DHE with inhaled DHE (Table 2). A greater incidence of adverse effects were apparent following IV dosing. To investigate pharmacologically-mediated adverse effect differences between (1) intravenous and (2) inhaled Dihydroergotamine Mesylate (DHE), biogenic amine receptor binding (serotonin (5-HT), adrenergic, dopaminergic) of dihydroergotamine mesylate *in vitro* was determined, based on concentrations corresponding to the $C_{max}$ levels reported following inhaled and intravenous (IV) dosing in a clinical study.

**[0105]** To investigate the unexpected result that the lower spikes of DHE may have resulted in a different receptor binding profile thus achieving efficacy, but avoiding side effects, a clinical investigation of receptor binding at the $C_{max}$ concentrations were undertaken.

**[0106]** Peak Plasma DHE concentrations ($C_{max}$) were determined from plasma samples (LC-MS/MS) following intravenous administration (1 mg) by infusion over 3 minutes, and from plasma samples (LC-MS/MS) following inhaled dosing (0.88 mg and 0.44 mg doses), where doses were given by multiple actuations from an inhaler over a period of 2-4 minutes. The inhaled doses represent the expected systemic delivered dose and were estimated from the fine particle dose delivered ex-actuator. The observed $C_{max}$ data is presented in Figure 2 for DHE. A similar approach was also taken with the primary metabolite, 8'-OH-DHE.

**[0107]** Table 3 presents *in vitro* concentrations equivalent to $C_{max}$. These concentrations were selected for receptor-binding investigations for both DHE and 8'-OH-DHE.

| Dose level | Dihydroergotamine Mesylate (pg/mL) | 8'-OH Dihydroergotamine (pg/mL) |
|---|---|---|
| 1 mg IV | 53,215 | 378 |
| 0.88 mg inhaled | 4,287 | 149 |
| 0.44 mg inhaled | 1,345 | 58 |

***Table 3.*** *Concentrations equivalent to peak plasma concentrations investigated for receptor binding.*

**Example 3: Serotonin, Adrenergic and Dopaminergic Receptor Binding by DHE at Concentrations Equivalent to Peak Plasma Concentrations**

**[0108]** Radioligand receptor binding assays clearly show that DHE exhibits wide ranging pharmacology at multiple receptor sites. (Figures 3-5.) For the majority of receptors, DHE achieves significant binding at concentrations equivalent to the IV $C_{max}$ whereas inhaled binding at each dose yields a different profile. In most instances, binding is reduced when non-IV methods are used to administer.

**[0109]** The anti-migraine efficacy of DHE is due to agonist activity at 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors. Figure 3 shows receptor binding data at various serotonergic receptor subtypes, indicating greater response at several subtypes for intravenous administration at $C_{max}$. The notation "(h)" represents cloned human receptor subtypes. Similar trends were observed for adrenergic and dopaminergic subtypes. Binding at these receptors is demonstrated with 100% binding at 5-$HT_{1B}$ following both 1 mg intravenous and 0.88 mg inhaled dosing. (Figure 3.) Following inhalation, however, apparent binding at 5-$HT_{1D}$ receptors is lower than IV. The long duration of DHE in circulation beyond $C_{max}$ likely is due to biphasic elimination. (Wyss, P.A., Rosenthaler, J., Nuesch, E., Aellig, W.H. Pharmacokinetic investigation of oral and IV dihydroergotamine in healthy subjects. Eur. J. Clin. Pharmacol. 1991;41:597-602). These results suggest that maximal receptor binding is not entirely necessary for the duration of clinical response.

**[0110]** As seen in Figures 3-5, the IV method of administration with the high $C_{max}$ which resulted in side effects, showed extensive binding at the dopaminergic and adrenergic receptors at concentrations equivalent to the peak plasma spikes ($C_{max}$) resulting from the IV

administration method. Figure 4 shows receptor binding data at adrenergic (left panel) and dopaminergic (right panel) receptors, indicating greater response at several subtypes for intravenous administration at $C_{max}$. The notation "(h)" represents cloned human receptor subtypes and "NS" indicates non-specific binding.

**[0111]** The dopaminergic receptors D1 and D2 are primarily responsible for nausea and emesis. Concentrations equivalent to the peak plasma spikes ($C_{max}$) resulting from the novel administration method that dampened and delayed the peak, as shown in Figure 2, significantly lowered dopaminergic receptor binding, specifically at D2 and D1, as shown in Figure 4, with the ultimate result of reducing nausea and emesis in the patients.

**[0112]** Similarly the lowered adrenergic binding shown in Figure 4, corresponded to less vasoconstriction and lowered blood pressure or cardiovascular excursions in the patients. While receptor binding at the adrenergic and dopaminergic receptors were lower at concentrations equivalent to the peak plasma spikes ($C_{max}$) resulting from the novel administration method, the binding achieved by these administration methods at the serotonin receptors, specifically $5HT_{1a/d}$ was sufficient to be efficacious for treatment of migraine. (Figure 3.)

**[0113]** Agonists of 5-$HT_{1B}$ subtype receptors are known to be useful in the treatment of migraine and associated symptoms. 5-$HT_{2B}$ receptors are known to play a triggering role in the onset of migraine. Figure 5 shows selective agonism at 5-$HT_{1B}$ and 5-$HT_{2B}$ receptors following high concentration control (5 μm), IV at $C_{max}$ (77.6 nM), 4 inhalations at $C_{max}$ (6.25 nM) and at a markedly reduced concentration (0.25 nM). Whereas 5-$HT_{1B}$ agonism is maintained across all concentrations, indicating high potency, agonism is absent for orally-inhaled DHE at the 5-$HT_{2B}$ receptors.

**[0114]** It is noted that all three methods of administration achieve rapid plasma levels within 20 minutes, with concentrations sufficient to bind the serotonin receptors and effect rapid treatment of migraine. (Figure 2).

### Example 4: Pulmonary Administration of DHE formulations using a TEMPO™ Inhaler

**[0115]** DHE powder is generated using supercritical fluid processes which offer significant advantages in the production of DHE particles for inhalation delivery and produce respirable particles of the desired size in a single step. (*see* WO2005/025506A2.) A property of processed DHE drug substance is that the supercritical fluid processed crystals have remarkably smooth

surfaces with low surface energies and therefore tend to disperse effectively in propellant based systems. A controlled particle size for the microcrystals was chosen to ensure that a significant fraction of DHE would be deposited in the lung.

**[0116]** A blend of two inert and non-flammable HFA propellants were selected as part of formulation development) for the drug product: HFA 134a (1,1,1,2-tetrafluoroethane) and HFA 227ea (1,1,1,2,3,3,3-heptafluoropropane). The finished product contained a propellant blend of 70:30 HFA 227ea:HFA 134a, which was matched to the density of DHE crystals in order to promote pMDI suspension physical stability. The resultant suspension did not sediment or cream (which can precipitate irreversible agglomeration) and instead existed as a suspended loosely flocculated system, which is easily dispersed when shaken. Loosely fluctuated systems are well regarded to provide optimal stability for pMDI canisters. As a result of the formulation's properties, the formulation contained no ethanol and no surfactants/stabilizing agents.

**[0117]** The DHE formulation was administered to patients using TEMPO$^{TM}$, a novel breath activated metered dose inhaler. TEMPO$^{TM}$ overcomes the variability associated with standard pressurized metered dose inhalers (pMDI), and achieve consistent delivery of drug to the lung periphery where it can be systemically absorbed. To do so, TEMPO$^{TM}$ incorporates four novel features: 1) breath synchronous trigger – can be adjusted for different drugs and target populations to deliver the drug at a specific part of the inspiratory cycle, 2) plume control - an impinging jet to slow down the aerosol plume within the actuator, 3) vortexing chamber – consisting of porous wall, which provides an air cushion to keep the slowed aerosol plume suspended and air inlets on the back wall which drive the slowed aerosol plume into a vortex pattern, maintaining the aerosol in suspension and allowing the particle size to reduce as the HFA propellant evaporates, and 4) dose counter - will determine the doses remaining and prevent more than the intended maximum dose to be administered from any one canister. Features 2 and 3 have been shown to dramatically slow the deposition and improve lung deposition of the Emitted Dose (ED), by boosting the Fine Particle Fraction (FPF).

**[0118]** All publications and patent applications cited in this specification are herein incorporated by reference in their entirety as if each individual publication or patent application is specifically and individually indicated to be incorporated by reference.

**[0119]** Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

# CLAIMS

What is claimed is:

1. A method for rapid treatment of migraine in an individual with DHE or salts, hydrates, polymorphs, prodrugs, ion pairs and metabolites thereof, while minimizing side effects, the method comprising:

administering to the individual an amount of a DHE formulation at a rate sufficient for obtaining relief from a migraine symptom,

wherein the amount and rate of DHE administration causes a significant reduction in a side effect.

2. The method of claim 1, wherein the amount and rate of DHE administration is sufficient to develop a circulating plasma concentration level of DHE such that DHE acts as an agonist against a serotonin receptor and provides relief from a migraine symptom,

and further wherein the circulating plasma concentration level of DHE remains below a level necessary for active binding to an adrenergic or dopaminergic or arterial constrictor serotonin receptor to cause a side effect.

3. The method of claim 1, wherein the side effect is selected from the group consisting of nausea, emesis, vasospasm, paraesthesia, hypertension, dizziness, anxiety, dyspnea, headache, flushing, diarrhea, rash, increased sweating, cardiac valvulopathy, pleural and retroperitoneal fibrosis, adverse cardiovascular effect, blood pressure instability and arterial constriction.

4. The method of claim 1, wherein the side effect is selected from the group consisting of nausea and emesis.

5. The method of claim 2, wherein the circulating plasma concentration level of DHE actively binds less than 50% of a dopaminergic receptor.

6. The method of claim 5, wherein the dopaminergic receptor is selected from the group consisting of $D_1$ and $D_2$.

7. The method of claim 5, wherein the side effect is selected from the group consisting of nausea and emesis.

8. The method of claim 2, wherein the circulating plasma concentration level of DHE actively binds less than 20% of a dopaminergic receptor.

9. The method of claim 8, wherein the dopaminergic receptor is selected from the group consisting of $D_1$ and $D_2$.

10. The method of claim 8, wherein the side effect is selected from the group consisting of nausea and emesis.

11. The method of claim 2, wherein the circulating plasma concentration level of DHE actively binds less than 20% of 5-$HT_3$ receptors.

12. The method of claim 11, wherein the side effect is nausea.

13. The method of claim 2, wherein the circulating plasma concentration level of DHE actively binds less than 20% of an arterial constrictor serotonin receptor.

14. The method of claim 13, wherein the arterial constrictor serotonin receptor is 5-$HT_{2A}$ receptor.

15. The method of claim 13, wherein the arterial constrictor serotonin receptor is 5-$HT_{2B}$ receptor.

16. The method of claim 13, wherein the side effect is selcted from the group consisting of vasoconstriction and cardiovascular conditions.

17. The method of claim 2, wherein the circulating plasma concentration level of DHE actively binds less than 60% of adrenergic receptors.

18. The method of claim 17, wherein the circulating plasma concentration level of DHE actively binds less than 20% of adrenergic receptors.

19. The method of claim 17, wherein the side effect is selcted from the group consisting of vasoconstriction, elevated blood pressure and cardiovascular conditions.

20. The method of claim 2, wherein the circulating plasma concentration level of DHE actively binds a serotonin receptor selected from the group consisting of 5-$HT_{1A}$, 5-$HT_{1B}$, and 5-$HT_{1D}$, at a level sufficient for obtaining relief from a migraine symptom.

21. The method of claim 1, wherein the DHE is administered at a rate such that the peak plasma concentration ($C_{max}$) is less than 15,000 pg/ml concentration in the circulating plasma in humans, and the time ($T_{max}$) following administration when the peak plasma concentration is attained, is less than 30 minutes after administration.

22. The method of claim 21, wherein the $C_{max}$ of DHE is less than 10,000 pg/mL in the circulating plasma.

23. The method of claim 21, wherein the $C_{max}$ of DHE is less than 7,500 pg/mL in the circulating plasma.

24. The method of claim 21, wherein the DHE is administered at a rate such that the $T_{max}$ of DHE is less than 20 minutes in the circulating plasma.

25. The method of claim 1, wherein the DHE is administered at a rate such that the peak plasma concentration ($C_{max}$) of DHE is at least 10-fold reduced from the $C_{max}$ of DHE administered by direct intravenous delivery.

26. The method of claim 1, wherein the DHE is administered at a rate such that the peak plasma concentration ($C_{max}$) of DHE is at least at least 1 minute delayed from the $T_{max}$ of DHE administered by direct intravenous delivery.

27. The method of claim 24, wherein the administration of DHE to achieve the $C_{max}$ and $T_{max}$ levels results in at least partial relief from a migraine syndrome selected from the group consisting of pain, nausea, phonophobia and photophobia, wherein the relief is achieved in 30 minutes or less, and further wherein drug-induced nausea, cardiovascular side effects or other adverse effects are reduced.

28. The method of claim 1, wherein the relief from a migraine syndrome is measured by a drop from a IHS score of greater than "0" for a migraine symptom at the time of administration of DHE, to a score of $\leq 1$ at 30, 60, 90 or 120 minutes following administration.

29. The method of claim 1, wherein an unit dose of less than 2.0 mg DHE or salts, hydrates, polymorphs prodrugs, ion pairs and metabolites thereof is administered.

30. The method of claim 14, wherein an unit dose of less than 2.0 mg DHE or salts, hydrates, polymorphs prodrugs, ion pairs and metabolites thereof is administered and an area the curve of the concentration of the drug in the systemic circulation versus time (AUC) of the drug delivered is within 75% of the comparable intravenous (IV) delivered dose.

31. The method of claim 1, wherein the administration results in a peak plasma concentration of a primary active metabolite of DHE of less than 1,000 pg/ml at $C_{max}$.

32. The method of claim 31, wherein the primary active metabolite of DHE is 8-hydroxy-dihydroergotamine.

33. The method of claim 31, wherein the $C_{max}$ of the primary metabolites is less than 500 pg/mL in the circulating plasma.

34. The method of claim 31, wherein the $C_{max}$ of the primary metabolites is less than 200 pg/mL in the circulating plasma.

35. The method of claim 31, wherein the $T_{max}$ of the primary metabolites is less than 90 minutes in the circulating plasma.

36. A formulation comprising DHE or salts, hydrates, polymorphs, prodrugs, ion pairs and metabolites thereof, wherein said formulation is suitable for administration according to the method of claim 1.

37. The formulation of claim 36, wherein administration of the DHE formulation in an amount sufficient to develop a circulating plasma concentration level of DHE effective as an agonist against a serotonin receptor such that a migraine symptom is alleviated, does not cause the circulating plasma concentration level of DHE to bind an adrenergic receptor or dopaminergic receptor or arterial constrictor serotonin receptor at a level that causes a side effect.

38. The method of claim 1, wherein the DHE formulation is administered by a mode selected from the group consisting of: intravenous, intra-arterial, intraperitoneal, intrapulmonary, oral, sublingual, buccal, intranasal, oral inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, iontophoresis, and transdermal administration.

39. The method of claim 38, wherein the DHE formulation is administered by pulmonary inhalation comprising aerosols, dry powder inhalers, nebulizers, vaporizers or pressurized metered dose inhalers (pMDI).

40. The method of claim 38, wherein the DHE formulation is administered by a breath activated metered dose inhaler.

41. The method of claim 1, wherein the DHE formulation is administered by a mode selected from the group consisting of: intravenous, intra-arterial, intraperitoneal, intrapulmonary, oral, sublingual, buccal, intranasal, oral inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, iontophoresis, and transdermal administration, and

further wherein the DHE is administered at a rate such that the peak plasma concentration ($C_{max}$) is less than 10,000 pg/ml concentration in the circulating plasma in humans, and the time ($T_{max}$) following administration when the peak plasma concentration is attained, is less than 30 minutes after administration.

42. The method of claim 41, wherein the DHE formulation is administered by pulmonary inhalation comprising aerosols, dry powder inhalers, nebulizers, vaporizers or pressurized metered dose inhalers (pMDI).

43. The method of claim 42, wherein the DHE formulation is administered by a breath activated metered dose inhaler.

44. The method of claim 43, wherein the DHE formulation is administered without administering an anti-emetic to the individual.

45. The method of claim 1, wherein the DHE formulation is administered to an individual by a breath activated metered dose inhaler,

wherein the DHE is administered at a rate such that the peak plasma concentration ($C_{max}$) is less than 10,000 pg/ml concentration in the circulating plasma in humans, and the time ($T_{max}$)

following administration when the peak plasma concentration is attained, is less than 20 minutes after administration, and

further wherein the DHE formulation is administered without administering an anti-emetic to the individual.

46. A kit comprising an unit dose of DHE or salts, hydrates, polymorphs, prodrugs, ion pairs and metabolites thereof, wherein the unit dose when administered to a human individual is sufficient for obtaining relief from a migraine symptom under conditiond where the amount and rate of DHE administration does not cause a side effect

47. The kit of claim 46, further comprising an inhaler device.

48. The kit of claim 46, further comprising a nebulizer.

49. The kit of claim 46, further comprising a pressurized metered dose inhaler.

50. An inhaler device comprising one or more unit doses of a DHE formulation wherein each unit dose is administered at a rate such that the peak plasma concentration ($C_{max}$) is less than 10,000 pg/ml concentration in the circulating plasma in humans, and the time ($T_{max}$) following administration when the peak plasma concentration is attained, is less than 30 minutes after administration.

51. The inhaler device of claim 50, wherein the DHE formulation is provided in a sealed container.

52. A method for rapid treatment of a disease or condition in an individual with a compound that (a) binds to one or more first receptors, wherein binding of the compound to the first receptors alleviates the disease or condition, and (b) binds to one or more second receptors, wherein binding of the compound to the second receptors causes a side effect, the method comprising:

administering to the individual an amount of the compound at a rate sufficient to develop a circulating plasma concentration level of the compound such that compound acts as an agonist against the first receptor and provides relief from the disease or condition,

wherein the circulating plasma concentration level of the compound remains below a level necessary for binding to the second receptor to cause a side effect.