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[Continued on next page]

(54) Title: DERMAL APPLICATION OF VASOCONSTRICTORS

(57) Abstract: There is disclosed the topical dermal use of vasoconstrictor substances for regulating body temperature to treat, prevent or delay the onset of anesthetic induced hypothermia. Kits containing appropriate materials and instructions, and other embodiments, are also disclosed.

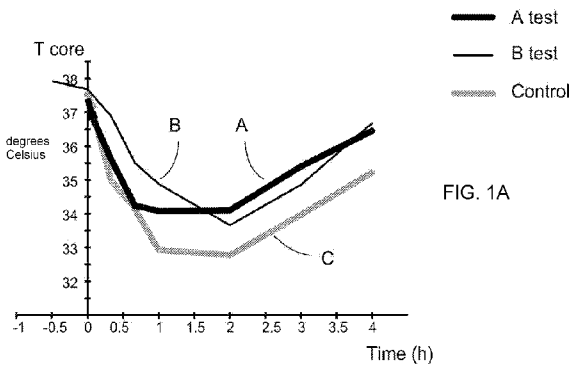

FIG. 1A

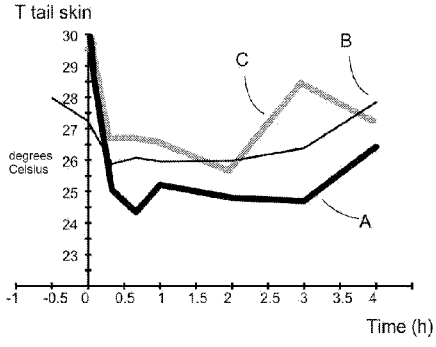

FIG. 1B

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DERMAL APPLICATION OF VASOCONSTRICTORS

[0001] This application claims priority from U.S. provisional application no. 61/118612, filed November 30, 2008, and from international application no. PCT/IL09/00652, filed June 30, 2009. The contents of these applications are incorporated herein by reference.

BACKGROUND

Postoperative Hypothermia (Anesthetic Induced Hypothermia)

[0002] The American Society of PeriAnesthesia Nurses defines normothermia as a core body temperature (CBT) ranging between 96.8°F and 100.4°F (36°C and 38°C), hyperthermia as a CBT greater than 38°C, and hypothermia as a core temperature lower than 96.8°F (36°C). Unplanned hypothermia is frequently a problem during or following surgery in which the patient has been administered a general anesthetic. Anesthetic-induced impairment of thermoregulatory control is the primary cause of postoperative hypothermia. Evidence is that the hypothermia starts to develop already during the surgical procedure after the start of administration of anesthesia (Good et al., *Association of Operating Room Nurses AORN Journal*, May 2006, 83:5, Health Module p.1055).

[0003] Hypothermia has been associated with a number of adverse consequences, including: increased risk of intra-operative blood loss; increased susceptibility to infection (such as myocardial ischemia); impaired coagulation and increased transfusion requirements; cardiovascular stress and cardiac complications; altered drug metabolism; postanesthetic shivering and thermal discomfort, as well as longer patient stays in the postanesthesia care unit (PACU) (Good et al., *AORN Journal,* May 2006; 83, 5; Health Module p. 1055).

[0004] Compared with normothermic patients, patients admitted to the intensive care unit (ICU) with a body core temperature (BCT) < 36°C have a significantly greater mortality, prolonged need for mechanical ventilation, incidence of packed red blood cell transfusion, and prolonged ICU and hospital length of stay (Insler et al., *The Annals of thoracic surgery,* 2000 Jul:175).

[0005] Methods for preventing anesthetic induced hypothermia commonly employ external heating devices (such as warming blankets, warm air blowers, and the like) and devices to reduce or prevent heat loss, such as light-reflecting covers. Unlike the heating devices used to induce hyperthermia, the heating devices used to treat or prevent anesthetic-induced hypothermia are necessarily designed to allow access to those portions of the patient body undergoing surgery.

[0006] Hence, it would be useful if there existed a method to treat or prevent anesthetic-induced hypothermia, which does not involve external devices which may be expensive and/or disturbing to the surgical team.

BRIEF DESCRIPTION OF EMBODIMENTS OF THE INVENTION

[0007] There is provided, in accordance with an embodiment of the invention, a method for treating, preventing or delaying the onset of anesthetic hypothermia, which comprises applying to the skin of a patient who is under general anesthetic or is about to be put under general anesthetic an amount of at least one vasoconstrictor effective to treat, prevent or delay the onset of anesthetic hypothermia. In some embodiments, the at least one vasoconstrictor is present as a mixture of vasoconstrictors. In some embodiments, the vasoconstrictor or mixture of vasoconstrictors is present in a pharmaceutical composition. In some embodiments, the pharmaceutical composition is applied to at least 10% of the patient's skin. In some embodiments, the pharmaceutical composition is applied to at least 15% of the patient's skin. In some embodiments, the pharmaceutical composition is applied to at least 20% of the patient's skin. In some embodiments, the pharmaceutical composition is applied to at least 25% of the patient's skin. In some embodiments, the pharmaceutical composition is applied to at least 30% of the patient's skin. In some embodiments, the pharmaceutical composition is applied to at least 35% of the patient's skin. In some embodiments, the pharmaceutical composition is applied to at least 40% of the patient's skin. In some embodiments, the pharmaceutical composition is applied to at least 45% of the patient's skin. In some embodiments, the pharmaceutical composition is applied to at least 50% of the patient's skin.

[0008] In some embodiments, the skin to which the at least one vasoconstrictor is applied includes skin selected from the group consisting of the palm of the hand, the sole of the foot, the ear, and the face. In some embodiments, the at least one vasoconstrictor is applied in the form of a dermally administrable pharmaceutical composition containing at least 1% by weight of the at least one vasoconstrictor. In some embodiments, the composition contains at least 2% by weight of the at least one vasoconstrictor. In some embodiments, the composition contains at least 3% by weight of the at least one vasoconstrictor. In some embodiments, the composition contains at least 4% by weight of the at least one vasoconstrictor. In some embodiments, the composition contains at least 5% by weight of the at least one vasoconstrictor. In some embodiments, the composition contains at least 10% by weight of the at least one vasoconstrictor. In some embodiments, the composition contains at least 20% by weight of the at least one vasoconstrictor. In some embodiments, the composition contains at least 25% by

weight of the at least one vasoconstrictor. In some embodiments, the composition contains at least 30% by weight of the at least one vasoconstrictor.

[0009] In some embodiments, at least two vasoconstrictors are used, each of the at least two vasoconstrictors having peak effectiveness at different times after administration. In some embodiments, at least two vasoconstrictors are used, each of the at least two vasoconstrictors exerting its vasoconstrictive effect via a different mechanism. In some embodiments, at least two vasoconstrictors are used, each of the at least two vasoconstrictors having a different duration of effectiveness after administration.

[0010] In some embodiments, at least one vasoconstrictor is selected from the group consisting of (i) the group consisting of vasoactive agonists, vasopressor agents and vasoconstrictor drugs; (ii) an agent that acts on vasopressin receptors or adrenoreceptors; (iii) a calcium channel agonist; (iv) an agonist of the α_1 adrenergic receptor; (v) alfuzosin, doxazosin, epinephrine, methoxamine, naphazoline, norepinephrine, phenylephrine, prazosin, terazosin, tetrahydrozaline, tamsulosin; (vi) an agonist of the $5HT_1B_AD$ receptor; (vii) almotriptan, avitriptan, frovatriptan, oxidesumitriptan, rizatriptan, zolmitriptan; (viii) chlorpheniramine, ethyinorephinephrine, mephenterine, metaraminol, oxymetazoline, oxymetazoline, phenylpropanolamine, potassium chloride, pseudoephidrine, propylhexadrine; (ix) ephedrine, angiotensin and vasopressin; (x) tetrahydrozoline HCl 0.05%, naphazoline HCl 0.03%, oxymetazoline HCl 0.025%; (xi) a vasoconstrictor extract selected from the group including ephedra sinica (ma huang), polygonum bistorta (bistort root), hamamelis virginiana (witch hazel), hydrastis canadensis (goldenseal), lycopus virginicus (bugleweed), aspidosperma quebracho (quebracho bianco), cytisus scoparius (scotch broom), guava extract, ellagic acid, caffeine, peppermint extract, chamomile oil, and cypress; (xii) an agent that positively affects the McKenzie vasoconstrictor assay; (xiii) topical corticosteroids, hydrocortisone, cortisol, synthetic corticosteroids, betametasone, fluticasone, mometasone; (xiv) antagonists of the β_2 adrenergic receptor, such as butaxamine.

[0011] In some embodiments, the at least one vasoconstrictor is selected from the group consisting of methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, metaraminol, 4-(1-naphthalen-1-ylethyl)-1H-imidazole (4-NEMD), clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, xylazine, methyldopa, apraclonidine, brimonidine, detomidine, dexmedetomidine, lofexidine, romifidine, tizanidine, xylometazoline, amidephrine, amitraz, anisodamine, ergotamine, indanidine, medetomidine, mephentermine, midodrine, mivazerol, naphazoline, norfenefrine, octopamine, phenylpropanolamine, rilmenidine, synephrine, talipexole, tetrahydrozoline, xylometazoline, dobutamine, dopamine, denopamine, xamoterol, salbutamol, levosalbutamol, fenoterol, terbutaline, pirbuterol, procaterol, bitolterol, rimiterol,

carbuterol, tulobuterol, reproterol, dopexamine, arformoterol, bambuterol, clenbuterol, formoterol, salmeterol, orciprenaline, metaproterenol, ritodrine, hexoprenaline, indacaterol, amibegron, solabegron, arbutamine, befunolol, isoxsuprine, nylidrin, oxyfedrine, prenalterol, ractopamine, bromoacetylalprenololmenthane, broxaterol, cimaterol, higenamine, mabuterol, methoxyphenamine, tretoquinol, zinterol isoprenaline, isoproterenol, epinephrine, norepinephrine, cirazoline, etilefrine, amphetamine, tyramine, ephedrine, pseudoephedrine, cocaine, allobarbital, amobarbital, aprobarbital, barbital, butobarbital, cyclobarbital, ethallobarbital, heptabarbital, hexobarbital, methohexital, pentobarbital, phenobarbital, proxibarbal, reposal, secobarbital, talbutal, thiopental, vinylbital, vinbarbital, brotizolam, cinolazepam, doxefazepam, estazolam, flunitrazepam, flurazepam, flutoprazepam, loprazolam, lormetazepam, nitrazepam, nimetazepam, midazolam, quazepam, temazepam, triazolam CL-218872, eszopiclone, indiplon, necopidem, pazinaclone, ROD-188, saripidem, suproclone, suriclone, SX-3228, U-89843A, U-90042, zaleplon, zolpidem, zopiclone, glutethimide, methyprylon, pyrithyldione afloqualone, cloroqualone, diproqualone, etaqualone, mebroqualone, mecloqualone, methaqualone, methylmethaqualone acebrochol, allopregnanolone, alphadolone, alphaxolone, ganaxolone, hydroxydione, minaxolone, Org 20599, tetrahydrodeoxycorticosterone, dexmedetomidine, lofexidine, medetomidine, romifidine, tizanidine, xylazine agomelatine, melatonin, ramelteon, doxylamine, hydroxyzine, diphenhydramine, bromodiphenhydramine, carbinoxamine, orphenadrine, niaprazine, phenyltoloxamine, propiomazine, pyrilamine, scopolamine, aceburic acid, gamma-amino-beta-hydroxybutyric acid (GABOB), gamma-hydroxybutyric acid (GHB), sodium oxybate, Xyrem®, gamma-butyrolactone (GBL), 1,4-butanediol, 3-chloropropanoic acid, acetylglycinamide chloral hydrate, chloral hydrate, chloralodol, dichloralphenazone, paraldehyde, petrichloral, centalun, ethchlorvynol, ethinamate, hexapropymate, methylpentynol, meprobamate, carisoprodol, tybamate, methocarbamol, 2-methyl-2-butanol, acecarbromal, apronal, bromisoval, carbromal, clomethiazole, embutramide, etomidate, gaboxadol, loreclezole, mephenoxalone, sulfonmethane, trichloroethanol, triclofos, valerian, valnoctamide and trazadone. In some embodiments, the at least one vasoconstrictor is selected from the group consisting of α_1 agonists and β_2 blockers. In some embodiments, the at least one vasoconstrictor is selected from the group consisting of epinephrine, norepinephrine, and pharmaceutically acceptable salts thereof.

[0012] In some embodiments, the at least one vasoconstrictor is applied in the form of a dermally administrable pharmaceutical composition that further comprises at least one of an antiseptic, antibiotic, antimycotic, or antiviral compound. In some embodiments, the at least one

vasoconstrictor is applied in the form of a dermally administrable pharmaceutical composition that further comprises a penetration enhancer.

[0013] In some embodiments, the at least one vasoconstrictor is applied in a concentration and to an amount of skin effective to raise the patient's core body temperature by 1°C within a period of 60 minutes from administration. In some embodiments, the at least one vasoconstrictor is applied in a concentration and to an amount of skin effective to raise the patient's core body temperature by at least 1°C for a period of at least 1 hour. In some embodiments, the at least one vasoconstrictor is applied in conjunction with at least one of (a) a penetration enhancer, (b) heat from an external source, and (c) a thermogenic substance. In some embodiments, one vasoconstrictor is used. In some embodiments, more than one vasoconstrictor is used. In some embodiments, a mixture of vasoconstrictors is used.

[0014] There is also provided, in accordance with an embodiment of the invention, a kit comprising at least one vasoconstrictor and instructions or a label explaining how to use the at least one vasoconstrictor to treat, prevent or delay the onset of anesthetic hypothermia in a patient. In some embodiments, the instructions or label instruct the user to apply the at least one vasoconstrictor to the skin of a patient who is under general anesthetic or is about to be put under general anesthetic in an amount effective to treat, prevent or delay the onset of anesthetic hypothermia. In some embodiments, the vasoconstrictor is present in a pharmaceutical composition. In some embodiments, the instructions or label instruct the user how to prepare a dermally administrable pharmaceutical composition containing the at least one vasoconstrictor. In some embodiments, the dermally administrable pharmaceutical composition contains at least 1% by weight of the at least one vasoconstrictor. In some embodiments, the dermally administrable pharmaceutical composition contains at least 2% by weight of the at least one vasoconstrictor. In some embodiments, the dermally administrable pharmaceutical composition contains at least 3% by weight of the at least one vasoconstrictor. In some embodiments, the dermally administrable pharmaceutical composition contains at least 4% by weight of the at least one vasoconstrictor. In some embodiments, the dermally administrable pharmaceutical composition contains at least 5% by weight of the at least one vasoconstrictor. In some embodiments, the dermally administrable pharmaceutical composition contains at least 10% by weight of the at least one vasoconstrictor. In some embodiments, the dermally administrable pharmaceutical composition contains at least 15% by weight of the at least one vasoconstrictor. In some embodiments, the dermally administrable pharmaceutical composition contains at least 20% by weight of the at least one vasoconstrictor. In some embodiments, the dermally administrable pharmaceutical composition contains at least 25% by weight of the at least one

vasoconstrictor. In some embodiments, the dermally administrable pharmaceutical composition contains at least 30% by weight of the at least one vasoconstrictor. In some embodiments, the instructions or label instruct the user and to apply the pharmaceutical composition to at least 10% of the patient's skin. In some embodiments, the instructions or label instruct the user and to apply the pharmaceutical composition to at least 15% of the patient's skin. In some embodiments, the instructions or label instruct the user and to apply the pharmaceutical composition to at least 20% of the patient's skin. In some embodiments, the instructions or label instruct the user and to apply the pharmaceutical composition to at least 25% of the patient's skin. In some embodiments, the instructions or label instruct the user to apply the pharmaceutical composition to at least 30% of the patient's skin. In some embodiments, the instructions or label instruct the user and to apply the pharmaceutical composition to at least 35% of the patient's skin. In some embodiments, the instructions or label instruct the user and to apply the pharmaceutical composition to at least 40% of the patient's skin. In some embodiments, the instructions or label instruct the user and to apply the pharmaceutical composition to at least 45% of the patient's skin. In some embodiments, the instructions or label instruct the user and to apply the pharmaceutical composition to at least 50% of the patient's skin. In some embodiments, the instructions or label instruct that the skin to which the vasoconstrictor is applied includes skin selected from the group consisting of the palm of the hand, the sole of the foot, the ear, and the face. In some embodiments, the composition further comprises a substance selected from the group consisting of a penetration enhancer, an antiseptic compound, an antibiotic compoud, an antimycotic compound, and an antiviral compound. In some embodiments, the kit comprises at least two vasoconstrictors, each of the at least two vasoconstrictors having peak effectiveness at different times after administration. In some embodiments, the kit comprises at least two vasoconstrictors, wherein each of the at least two vasoconstrictors exerts its vasoconstrictive effect via a different mechanism. In some embodiments, the kit comprises at least two vasoconstrictors, each of the at least two vasoconstrictors having a different duration of effectiveness after administration.

[0015] In some embodiments, the at least one vasoconstrictor is selected from the group consisting of (i) the group consisting of vasoactive agonists, vasopressor agents and vasoconstrictor drugs; (ii) an agent that acts on vasopressin receptors or adrenoreceptors; (iii) a calcium channel agonist; (iv) an agonist of the α_1 adrenergic receptor; (v) alfuzosin, doxazosin, epinephrine, methoxamine, naphazoline, norepinephrine, phenylephrine, prazosin, terazosin, tetrahydrozaline, tamsulosin; (vi) an agonist of the $5HT_1B_AD$ receptor; (vii) almotriptan, avitriptan, frovatriptan, oxidesumitriptan, rizatriptan, zolmitriptan; (viii) chlorpheniramine,

ethyinorephinephrine, mephenterine, metaraminol, oxymetazoline, oxymetazoline, phenylpropanolamine, potassium chloride, pseudoephidrine, propylhexadrine; (ix) ephedrine, angiotensin and vasopressin; (x) tetrahydrozoline HCl 0.05%, naphazoline HCl 0.03%, oxymetazoline HCl 0.025%; (xi) a vasoconstrictor extract selected from the group including ephedra sinica (ma huang), polygonum bistorta (bistort root), hamamelis virginiana (witch hazel), hydrastis canadensis (goldenseal), lycopus virginicus (bugleweed), aspidosperma quebracho (quebracho bianco), cytisus scoparius (scotch broom), guava extract, ellagic acid, caffeine, peppermint extract, chamomile oil, and cypress; (xii) an agent that positively affects the McKenzie vasoconstrictor assay; (xiii) topical corticosteroids, hydrocortisone, cortisol, synthetic corticosteroids, betametasone, fluticasone, mometasone; (xiv) antagonists of the β2 adrenergic receptor, such as butaxamine.

[0016] In some embodiments, the at least one vasoconstrictor is selected from the group consisting of methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, metaraminol, 4-(1-naphthalen-1-ylethyl)-1H-imidazole (4-NEMD), clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, xylazine, methyldopa, apraclonidine, brimonidine, detomidine, dexmedetomidine, lofexidine, romifidine, tizanidine, xylometazoline, amidephrine, amitraz, anisodamine, ergotamine, indanidine, medetomidine, mephentermine, midodrine, mivazerol, naphazoline, norfenefrine, octopamine, phenylpropanolamine, rilmenidine, synephrine, talipexole, tetrahydrozoline, xylometazoline, dobutamine, dopamine, denopamine, xamoterol, salbutamol, levosalbutamol, fenoterol, terbutaline, pirbuterol, procaterol, bitolterol, rimiterol, carbuterol, tulobuterol, reproterol, dopexamine, arformoterol, bambuterol, clenbuterol, formoterol, salmeterol, orciprenaline, metaproterenol, ritodrine, hexoprenaline, indacaterol, amibegron, solabegron, arbutamine, befunolol, isoxsuprine, nylidrin, oxyfedrine, prenalterol, ractopamine, bromoacetylalprenololmenthane, broxaterol, cimaterol, higenamine, mabuterol, methoxyphenamine, tretoquinol, zinterol isoprenaline, isoproterenol, epinephrine, norepinephrine, cirazoline, etilefrine, amphetamine, tyramine, ephedrine, pseudoephedrine, cocaine, allobarbital, amobarbital, aprobarbital, barbital, butobarbital, cyclobarbital, ethallobarbital, heptabarbital, hexobarbital, methohexital, pentobarbital, phenobarbital, proxibarbal, reposal, secobarbital, talbutal, thiopental, vinylbital, vinbarbital, brotizolam, cinolazepam, doxefazepam, estazolam, flunitrazepam, flurazepam, flutoprazepam, loprazolam, lormetazepam, nitrazepam, nimetazepam, midazolam, quazepam, temazepam, triazolam CL-218872, eszopiclone, indiplon, necopidem, pazinaclone, ROD-188, saripidem, suproclone, suriclone, SX-3228, U-89843A, U-90042, zaleplon, zolpidem, zopiclone, glutethimide, methyprylon, pyrithyldione afloqualone, cloroqualone, diproqualone, etaqualone, mebroqualone,

mecloqualone, methaqualone, methylmethaqualone acebrochol, allopregnanolone, alphadolone, alphaxolone, ganaxolone, hydroxydione, minaxolone, Org 20599, tetrahydrodeoxycorticosterone, dexmedetomidine, lofexidine, medetomidine, romifidine, tizanidine, xylazine agomelatine, melatonin, ramelteon, doxylamine, hydroxyzine, diphenhydramine, bromodiphenhydramine, carbinoxamine, orphenadrine, niaprazine, phenyltoloxamine, propiomazine, pyrilamine, scopolamine, aceburic acid, gamma-amino-beta-hydroxybutyric acid (GABOB), gamma-hydroxybutyric acid (GHB), sodium oxybate, Xyrem®, gamma-butyrolactone (GBL), 1,4-butanediol, 3-chloropropanoic acid, acetylglycinamide chloral hydrate, chloral hydrate, chloralodol, dichloralphenazone, paraldehyde, petrichloral, centalun, ethchlorvynol, ethinamate, hexapropymate, methylpentynol, meprobamate, carisoprodol, tybamate, methocarbamol, 2-methyl-2-butanol, acecarbromal, apronal, bromisoval, carbromal, clomethiazole, embutramide, etomidate, gaboxadol, loreclezole, mephenoxalone, sulfonmethane, trichloroethanol, triclofos, valerian, valnoctamide and trazadone. In some embodiments, the at least one vasoconstrictor is selected from the group consisting of α_1 agonists and β_2 blockers. In some embodiments, the at least one vasoconstrictor is selected from the group consisting of epinephrine, noepinephrine, and pharmaceutically acceptable salts thereof.

[0017] In some embodiments, the instructions or label explain how to apply the at least one vasoconstrictor in a concentration and to an amount of skin effective to raise the patient's core body temperature by 1°C within a period of 60 minutes. In some embodiments, the instructions or label instruct the user to apply the at least one vasoconstrictor in conjunction with the dermal application of at least one of an antiseptic, antibiotic, an antimycotic or an antiviral compound. In some embodiments, the kit further comprises at least one of an antiseptic, antibiotic, an antimycotic or an antiviral compound. In some embodiments, the label or instructions explain how to apply the at least one vasoconstrictor in conjunction with a penentration enhancer. In some embodiments, the kit further comprises a penetration enhancer. In some embodiments, the kit contains one vasoconstrictor. In some embodiments, the kit contains more than one vasoconstrictor. In some embodiments, the kit contains a mixture of vasoconstrictors.

DETAILED DESCRIPTION

[0018] In one aspect, there are provided in accordance with embodiments of the invention methods for treating, preventing or delaying the onset of anesthetic-induced hypothermia, by applying to the skin of a patient who is about to or who has already received general anesthetic at least one vasoconstrictor. In the context of this patent application, reference to "at least one

vasocontrictor" will be understood as also encompassing a plurality of vasoconstrictors, including mixtures of vasoconstrictors, unless noted otherwise. Thus, for example, if it is stated that a composition containing the at least one vasoconstrictor is applied to at least 10% of a patient's skin, this includes the situation in which one composition comprising a first vasoconstrictor is applied to 5% of the patient's skin and a second composition comprising a second vasoconstrictor is applied to another 5% of the patient's skin. Furthermore, in cases where it is stated that the at least one vasoconstrictor is selected from a closed group of substances, it will be understood that if the at least one vasoconstrictor is utilized as one of a plurality of vasoconstrictors, separately or in a mixture, only one of the vacoconstrictors in the plurality need necessarily be selected from the members of the closed group.

[0019] Body thermoregulation involves three primary elements: heat production due to core body functioning, heat loss mostly through the skin surface organ, and regulatory signals from the hypothalamus brain organ. The different aspects and embodiments of the present invention use vasocontrictor substances to substantially reduce body heat loss to the environment through the skin. Use of additional supportive or enhancing elements in accordance with some embodiments, such as stimulation of core body functions and/or suppression of hypothalamus control and/or suppression of perspiration, are discussed herein in the context of specific applications and embodiments.

[0020] Vasoconstrictor substances *per se* – i.e. compounds that cause constriction of the blood vessels – are known in the art, but have not hitherto been used or suggested to be used in accordance with the different aspects of the invention described herein. For example, PCT patent publication WO 2006/138691 (hereinafter "PCT2006") discloses pharmaceutical preparations containing vasoconstrictors and the use thereof to protect cells from the toxic side-effects of radiotherapy and cancer chemotherapeutic agents. Vasoconstrictor substances used in accordance with the teaching of PCT2006 are preferably agonists of the α_1 adrenergic receptor (preferred embodiments of which are stated to be epinephrine, phenylephrine, methoxamine, norepinephrine, tetrahydrozaline, naphazoline, prazosin, doxazosin, terazosin, alfuzosin, tamsulosin or any combination thereof) or agonists of the $5HT_1B_AD$ receptor (preferred embodiments of which are stated to be zolmitriptan, oxidesumitriptan, avitriptan, rizatriptan, almotriptan, frovatriptan, or any combination thereof). PCT2006 further teaches dosages of preferred embodiments.

[0021] US Patent No. 4978332 discusses local use of vasoconstrictors to inhibit the migration of cytotoxic drugs used for chemotherapy from the site of application of the cytotoxic drugs, by

altering the blood flow serving the tumor/lesion area, so as to maintain the primary effect of the cytotoxic drug at the site of application.

[0022] Vasoconstrictive agents are described in Medical Pharmacology (1984), C. V. Mosby, Company, Chapter 15.

[0023] US Patent Publication Number 20030216364 teaches a topical dermatological composition with improved vasoconstrictor properties.

[0024] PCT patent publication WO 2004/032888 teaches a shaving cream composition containing a vasoconstrictor substance for preventing bleeding from nicks and cuts that occur while shaving the face, wherein the vasoconstrictor is phenylephrine, ephinephrine, norephinephrine, ethyinorephinephrine, potassium chloride, methoxamine, oxymetazoline), chlorpheniramine, phenylpropanolamine, tetrahydrozoline, pseudoephidrine, mephenterine, metaraminol, propylhexadrine, oxymetazoline, naphalozine, or a combination thereof, or a derivative of one of these compounds which functions as a vasocontrictor.

[0025] US Patent Publication Number 20070048234 teaches methods for treating acne using a vasoconstrictor in conjunction with an anti-acne agent, wherein said vasoconstrictor is selected from the group consisting of tetrahydrozoline HCl 0.05%, naphazoline HCl 0.03%, oxymetazoline HCl 0.025%, guava extract, ellagic acid, caffeine, cypress oil, witch hazel, peppermint extract, chamomile oil, and bugleweed.

[0026] PCT patent publication number WO 2007/023396 teaches a therapeutic kit to provide a safe and effective dosage of a vasoactive agent, including an aerosol packaging assembly, wherein the vasoconstrictor is selected from the group consisting of: I. the group of vasoactive agonists, vasopressor agents and vasoconstrictor drugs; II. an agent that acts on vasopressin receptors or adrenoreceptors; III. a calcium channel agonist; IV. a vasoconstrictor selected from the group including ephedrine, epinephrine, phenylephrine, angiotensin and vasopressin; V. a vasoconstrictor selected from the group including ephedra sinica (ma huang), polygonum bistorta (bistort root), hamamelis virginiana (witch hazel), hydrastis canadensis (goldenseal), lycopus virginicus (bugleweed), aspidosperma quebracho (quebracho bianco), cytisus scoparius (scotch broom) and cypress; and VI. an agent that positively affects the McKenzie vasoconstrictor assay, and salts thereof.

[0027] PCT patent publication number WO 2006/031555 teaches cosmetically acceptable compositions which are particularly suited for skin lightening and for diminishing the appearance of 'dark circles' under the eyes. The compositions include any of several vasoconstrictors in a carrier with optionally added skin compatible ingredients.

[0028] Illustrative vasoconstrictive agents are: (1) sympathomimetics including the catecholamines, norepinephrine, epinephrine, isoproterenol, dopamine, and related compounds such as ephedrine and other phenylisopropylamines, phenylephrine, amphetamine, metraminol, methoxamine; (2) ergot alkaloids including lysergic acid, lysergic acid diethylamine, ergonovine, methylergonavine, methysergide, ergotamine; (3) the angiotensins; and (4) the prostaglandins. Vasoconstrictive agents are described in Medical Pharmacology (1984), C. V. Mosby, Company, Chapter 15.

[0029] The vasoconstrictor effect of topical corticosteroids, including its "skin blanching effect", is discussed in the article by Smith et al. in Dermatology, 205 pp. 3-10 (2002). Topical corticosteroids include hydrocortisone, cortisol, and synthetic corticosteroids such as betamethasone, fluticasone and mometasone. They are applied to the skin in the form of creams, ointments and lotions and are the mainstay of controlling flare-ups of eczema. An advantage of corticosteroids in comparison to some other dermally-applied vasoconstrictors is in their multiple hours of effectiveness (about 10 hours).

[0030] Another group of compounds that act as vasoconstrictors are α-adrenoceptor agonists and antagonists. Initially classified as either α or β subtype receptors, based on anatomical location and functional considerations, more recent pharmacological and molecular biological techniques have identified the heterogeneity of the α-adrenoceptors and led to the identification of numerous subtypes of each receptor. α-Adrenoceptors exist on peripheral sympathetic nerve terminals and are divided into two subtypes, α_1 and α_2. α_1 is found mostly postsynaptically, while α_2, although typically sited presynaptically, can also occur postsynaptically. These initial subtypes were further divided into α_{1A}, α_{1B} and α_{1D} receptors (by pharmacological methods), each with distinct sequences and tissue distributions, and α_{1a}, α_{1b}, and α_{1d} by molecular biological and cloning techniques (note lower case letters refer to cloned receptors). Similarly, work done to identify subtypes of the α_2 adrenoeceptor has led to the discovery of a subclasses α_{2A}, α_{2B}, α_{2C}, α_{2D}, and α_{2C10}.

[0031] α_1-adrenoceptors are found both in the central and peripheral nervous system. In the central nervous system they are found mostly postsynaptically and have an excitatory function. Peripherally, they are responsible for contraction and are situated on vascular and non-vascular smooth muscle. α_1-adrenoceptors on vascular smooth muscle are located intrasynaptically and function in response to neurotransmitter release. For non-vascular smooth muscle, they can be found on the liver, where they cause hepatic glycogenolysis and potassium release. On heart muscle they mediate a stimulatory (positive inotropic) effect. In the gastrointestinal system they cause relaxation of gastrointestinal smooth muscle and decrease salivary secretion.

[0032] The clinical uses of adrenergic compounds are vast. The treatment of many medical conditions can be attributed to the action of drugs acting on adrenergic receptors. For example, α-adrenoceptor ligands can be used in the treatment of hypertension. Drugs such as prazosin, an α_1-adrenoceptor antagonist and clonidine, an α_2-adrenoceptor agonist, both have antihypertensive effects. α_1-adrenoceptor antagonists are also employed in the treatment of benign prostatic hypertrophy.

TABLE 1

Receptor Type	α_1	A_2
Selective Agonist	Phenylephrine, Methoxamine, Methylnorepinephrine, Oxymetazoline	Clonidine, Clenbuterol
Selective Antagonist	Doxazosin, Prazosin	Yohimbine, Idazoxan
Second Messengers and Effectors	PLC activation via Gp/q Causes increases $[Ca^{2+}]_I$	decreases cAMP via Gi/o, causes decrease in $[Ca^{2+}]_I$
Physiological Effect	Smooth muscle contraction	Inhibition of transmitter release, Hypotension, anaesthesia, Vasoconstriction

[0033] Several sympathomimetic drugs are used primarily as vasoconstrictors for local application to nasal and ocular mucous membranes (see Table 1). α-adrenoceptor agonists are used extensively as nasal decongestants in patients with allergic or vasomotor rhinitis and in acute rhinitis in patients with upper respiratory infections (Empey et al., Drugs, June 1981, **21**(6):438-443). These drugs probably decrease the resistance to airflow by decreasing the volume of the nasal mucosa. The receptors that mediate this effect appear to be the α_1-adrenoceptors, though α_2-adrenoceptors may be responsible for contraction of arterioles that supply the nasal mucosa. While a major limitation of therapy with nasal decongestants is that of a loss of efficacy with prolonged use, agonists that are selective for α_1 receptors may be less likely to induce mucosal damage (DeBernadis et al. 1987). As an ocular decongestant, to decrease swelling and redness of the eyes, α-adrenoceptor agonists are widely used in the treatment of allergic conjunctivitis, whether seasonal (hay fever) or perennial.

[0034] The following is a non-exhaustive list of α- and β-adrenergic receptor agonists.

[0035] α_1 adrenergic receptor agonists: methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, metaraminol

[0036] α_2 adrenergic receptor agonists: 4-(1-naphthalen-1-ylethyl)-1H-imidazole (4-NEMD), clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, xylazine, methyldopa, apraclonidine, brimonidine, detomidine, dexmedetomidine, lofexidine, romifidine, tizanidine, xylometazoline, amidephrine, amitraz, anisodamine, ergotamine, indanidine, medetomidine,

mephentermine, midodrine, mivazerol, naphazoline, norfenefrine, octopamine, phenylpropanolamine, rilmenidine, synephrine, talipexole, tetrahydrozoline, xylometazoline, dexmedetomidine, lofexidine, romifidine, tizanidine, xylazine

[0037] β_1 adrenergic receptor agonists: dobutamine, dopamine, denopamine, xamoterol

[0038] β_2 adrenergic receptor short acting agonists: sulbutamol, levosalbutamol, fenoterol, terbutaline, pirbuterol, procaterol, bitolterol, rimiterol, carbuterol, tulobuterol, reproterol, dopexamine

[0039] β_2 adrenergic receptor long acting agonists (LABA): arformoterol, bambuterol, clenbuterol, formoterol, salmeterol, orciprenaline, metaproterenol, ritodrine, hexoprenaline, indacaterol

[0040] β_3 adrenergic receptor agonists: amibegron, solabegron, arbutamine, befunolol, isoxsuprine, nylidrin, oxyfedrine, prenalterol, ractopamine, bromoacetylalprenololmenthane, broxaterol, cimaterol, higenamine, mabuterol, methoxyphenamine, tretoquinol, zinterol

[0041] Nonselective β adrenergic receptor agonists: isoprenaline, isoproterenol

[0042] Dual α/β adrenergic receptor agonists: epinephrine {α_{1+2}, β_{1+2}}, norepinephrine {α_{1+2}, β_1}, cirazoline, etilefrine,

[0043] Indirect/mixed indirect presynaptic norepinephrine release: amphetamine, tyramine

[0044] Mixed: ephedrine, pseudoephedrine, cocaine, allobarbital, amobarbital, aprobarbital, barbital, butobarbital, cyclobarbital, ethallobarbital, heptabarbital, hexobarbital, methohexital, pentobarbital, phenobarbital, proxibarbal, reposal, secobarbital, talbutal, thiopental, vinylbital, vinbarbital; brotizolam, cinolazepam, doxefazepam, estazolam, flunitrazepam, flurazepam, flutoprazepam, loprazolam, lormetazepam, nitrazepam, nimetazepam, midazolam, quazepam, temazepam, triazolam; CL-218,872, eszopiclone, indiplon, necopidem, pazinaclone, ROD-188, saripidem, suproclone, suriclone, SX-3228, U-89843A, U-90042, zaleplon, zolpidem, zopiclone; glutethimide, methyprylon, pyrithyldione; afloqualone, cloroqualone, diproqualone, etaqualone, mebroqualone, mecloqualone, methaqualone, methylmethaqualone; acebrochol, allopregnanolone, alphadolone, alphaxolone, ganaxolone, hydroxydione, minaxolone, Org 20599, tetrahydrodeoxycorticosterone; melatonin, agomelatine, ramelteon; doxylamine, hydroxyzine, diphenhydramine, bromodiphenhydramine, carbinoxamine, orphenadrine, niaprazine, phenyltoloxamine, propiomazine, pyrilamine, scopolamine; aceburic acid, gamma-amino-beta-hydroxybutyric acid (GABOB), gamma- hydroxybutyric acid (GHB), sodium oxybate, Xyrem®, gamma-butyrolactone (GBL), 1,4-Butanediol, 3-Chloropropanoic acid; acetylglycinamide, chloral hydrate, chloralodol, dichloralphenazone, paraldehyde, petrichloral; centalun, ethchlorvynol, ethinamate, hexapropymate, methylpentynol; meprobamate,

carisoprodol, tybamate, methocarbamol; 2-methyl-2-butanol, acecarbromal, apronal, bromides, bromisoval, carbromal, clomethiazole, embutramide, etomidate, gaboxadol, loreclezole, mephenoxalone, sulfonmethane, trichloroethanol, triclofos, valerian, valnoctamide, trazadone.

[0045] Other non-limiting examples of vasoconstricting agents contemplated for use in accordance with embodiments of the invention include tetrahydrozoline HCl 0.05%, naphazoline HCl 0.03%, oxymetazoline HCl 0.025%, guava extract, ellagic acid, caffeine, cypress oil, hamamelis (witch hazel), peppermint extract, chamomile oil, and bugleweed.

[0046] In some embodiments, the vasoconstrictor is selected from the group consisting of methoxamine, phenylephrine, 4-NEMD, clonidine, methyldopa, dobutamine, salbutamol, terbutaline, and isoprenaline.

[0047] Skin Penetration Enhancers. In some embodiments of the invention, a penetration enhancer is used to facilitate the penetration of vasoconstrictor into the skin. Some techniques for improving the delivery of drugs through the skin are discussed in Benson, *Current Drug Delivery*, 2005, **2**:23-33. Suitable skin penetration enhancers include, for example, surfactants such as sodium laurate, sodium lauryl sulfate, cetyltrimethylammonium bromide, benzalkonium chloride, Poloxamer (231, 182, 184), Tween (20, 40, 60, 80) and lecithin (U.S. Pat. No. 4,783,450); the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one; alcohols such as ethanol, propanol, octanol, benzyl alcohol, and the like; fatty acids such as lauric acid, oleic acid and valeric acid; fatty acid esters such as isopropyl myristate, isopropyl palmitate, methylpropionate, and ethyl oleate; polyols and esters thereof such as propylene glycol, ethylene glycol, glycerol, butanediol, polyethylene glycol, and polyethylene glycol monolaurate; amides and other nitrogenous compounds such as urea, dimethylacetamide (DMA), dimethylformamide (DMF), 2-pyrrolidone, 1-methyl-2-pyrrolidone, ethanolamine, diethanolamine and triethanolamine; terpenes; alkanones; organic acids, particularly salicylic acid and salicylates, citric acid and succinic acid.

[0048] Generally, vasoconstrictors in accordance with embodiments of this invention may be dissolved in an appropriate pharmaceutically or cosmetically acceptable solvent and applied directly to the skin. In some embodiments, the vasoconstrictors are combined with a cream or gel base, so that application of the vasoconstrictor is more easily localized and controlled. Most pharmaceutically or cosmetically acceptable gel or cream bases may be used. Suitable gels include, for example, cellulose-based gels, (e.g., hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), and carboxymethyl cellulose (CMC)) and acrylate copolymers. Suitable cream bases include emulsions formed from a water phase of a humectant, a viscosity stabilizer and water, an oil phase of fatty acid alcohol, a semi-solid petroleum hydrocarbon and an emulsifying

agent and a phase containing the vasoconstrictor of the invention dispersed in an aqueous stabilizer-buffer solution. If desired, stabilizers, such as are known in the art or may be developed later, may be added in accordance with embodiments of the invention. Cream-based pharmaceutical formulations containing the vasoconstrictor may be contain, for example, aqueous emulsions containing a fatty acid alcohol, semi-solid petroleum hydrocarbon, 1,2-ethyleneglycol and an emulsifying agent.

[0049] In the context of this patent application, a "thermogenic substance" refers to a substance which increases the metabolism of the body, thereby generating heat. Common natural thermogenic substances are ephedra, bitter orange, capsicum, ginger and caffeine. The ECA Stack (ephedrine, caffeine, aspirin) is the most well-known thermogenic formulation, popular among bodybuilders as a means to achieve low body fat levels.

[0050] Substances which block α_2 adrenoreceptors, in addition to functioning as vasoconstrictors, may in some cases also act as thermogenic substances. For example, yohimbine works by blocking α_2 adrenoreceptors. There are a number of feedback mechanisms that prevent the release of norepinephrine (NE), one of the body's primary lipolytic hormones. When NE is released, such as in periods of stress or after taking a sympathomimetic (such as ephedrine), it stimulates both the α and β adrenoreceptors. Stimulation of the beta adrenoreceptors causes the breakdown of fat while stimulating the α_2 adrenoreceptors has the opposite effect, preventing the release of NE and lipolysis. Yohimbine prevents this negative feedback mechanism, thus increasing NE release and lipolysis. There are reasons why α_2 inhibition is specifically useful. While the β-adrenergic system primarily controls lipolysis during periods of intense activity, during rest, which makes up most of our day, the α-adrenergic system is in control. The increase of lipolysis is tantamount to thermogenesis. Therefore, α_2 blockers in general and Yohimbine in particular, are considered thermogenic substances in the present application.

[0051] Some substances may be thermogenic substances in one context but vasoconstrictors in another context. For example, caffeine, when ingested orally and absorbed into the core body blood stream, has the effect of increasing body metabolism, thereby being thermogenic, and dilating the core blood vessels. However, when applied dermally, caffeine has the effect of constricting cutaneous blood vessels.

[0052] Another dual action substance is ephedrine, an alkaloid from the leaves of *Ephedra equisetina*, *E. sinica*, and other species (family Gnetaceae), or produced synthetically; commonly used salts are ephedrine hydrochloride and ephedrine sulfate. Ephedrine is an adrenergic (sympathomimetic) agent, an alpha- and beta-adrenergic agonist, that may also

enhance release of norepinephrine. Its actions similar to those of epinephrine. When inhaled, it is used as a bronchodilator, mydriatic, or pressor agent. When used topically on skin, it is a vasoconstrictor.

[0053] Circulation through the skin serves two major functions: nutrition of the skin tissue and heat transfer. These two functions have different hemodynamic requirements. Nutrient exchange requires slow movement of blood through thin-walled, small diameter vessels with walls permeable to small molecules. Heat exchange requires the movement of large volumes of blood through vessels closely at or near a body surface. Accordingly, two types of vascular structures are found in the skin of mammals: 1) nutritive units consisting of arterioles, capillaries, and venules, and 2) heat-transfer units consisting of venous plexuses (dense networks of thick-walled, large-diameter venules) and arteriovenous anastomoses (AVAs; vascular communications between small arteries and the venous plexuses).

[0054] The heat-transfer vascular units and nutrient vascular units are anatomically distinct and have mutually exclusive functions. Nutritive vascular units are uniformly distributed throughout the skin, whereas the heat exchange units are found only in non-insulated skin regions; in humans these are the palms of the hands, the soles of the feet, the ears, and non-hairy regions of the face (Bergersen, 1993; Gemmell and Hales, 1977; Saad, 2001). Heat exchange units also exist in the footpads and tongues of dogs (Baker, 1982), ears of elephants (Phillips and Heath, 1992) and rabbits (Ootsuka et al., 2003), and tails of rodents (Heath, 1998, Johnson 2002). In the human hand, AVAs and associated venous plexuses are found under the nail beds, the tips of the digits, the palm, and the palmar surface of the fingers. AVAs and venous plexuses are absent from the dorsal surface of the fingers and hand (Roddie, 1983). The dimensions of venous plexuses determine the blood volume capacity of a heat exchange region while the AVAs control the blood flow through the venous plexuses. The heat exchange-vascular units do not contribute to the nutrition of surrounding tissues, and the nutritive units are not directly active in temperature regulation. The thermoregulatory vascular units enable direct heat transfer from the body core to the surrounding environment (Krauchi et al., 1999, 2000). Blood passing through these heat exchange units is delivered directly from the heart via the arterial system and is delivered back to the heart via venous return. Blood flow through the heat exchange vascular units is extremely variable. It has been estimated that blood flow into the venous plexuses can range from near zero in cold stress to as much as 60% of the total cardiac output during heat stress (Greenfield, 1983; Johnson and Proppe, 1996). Constriction of the AVAs helps to thermally isolate the body core from the environment. Conversely, dilation of the AVAs promotes a free exchange of heat between the body core and the environment. Consequently, in

accordance with some embodiments of the invention, the vasoconstrictor substance is an AVA constrictor.

[0055] Studies have shown that several 5-$HT_{1B/1D}$ receptor agonists potently constrict porcine carotid arteriovenous anastomoses, and it is likely that the same is true for humans. Such agonists include sumatriptan and alniditan (De Vries et al., Eur. J. Pharmacol. 1998 **351**:193-201). In another study, it was found that adrenergic α_1-stimulation with phenylephrine produced AVA constriction. Adrenergic α_2-stimulation with UK-14304 (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine) produced constriction of the AVA, norepinephrine (a mixed α_1- and α_2-agonist) also produced AVA vasoconstriction. Overall, AVAs contain a heterogeneous mixture of both α_1-and α_2-receptors, and α_2-receptors may have a greater influence than α_1-receptors on overall tone in AVA (Pollock et al., Am. J. Physiology, Heart and Circulatory Physiology, 1996, **40**:5, pp. H2007).

[0056] In accordance with some embodiments, the one or more vasoconstrictor substances are administered topically to the skin. This method of administration decreases systemic effects of the vasoconstrictors, limiting the constriction of interal blood vessels and concentrating the vasoconstriction near the area of application.

[0057] To be effective as a stand-alone, full body thermoregulating method, dermal administration of vasoconstrictor substances needs to be conducted over a substantial portion of the skin surface of the human body. Hence, an associated kit may contain (i) sufficient quantities of vasoconstrictor substance in a form appropriate for topical application, such as a gel, cream, foam, or ointment (or powder suitable for mixture within a liquid), and/or (ii) appropriate instructions.

[0058] Hypothermia is defined as body temperature below 36°C. Hence, in the context of the present invention, treating hypothermia should be understood as raising core body from a temperature below 36°C to a temperature of at least 36°C, and preventing hypothermia should be understood as maintaining core body temperature at or above 36°C.

[0059] Prevention and amelioration of hypothermia due to general anesthesia. With regard to post-operative hypothermia induced by anesthetic, in accordance with embodiments of the present invention, application of vasoconstrictor substances to the skin of patients can be used to induce vasoconstriction in the skin to prevent or ameliorate hypothermia. Application of the vasoconstrictor make take place shortly prior to the start of surgery, e.g. within 30-60 minutes of the commencement of surgery, thereby providing prophylaxis of hypothermia; or it may be conducted during or after surgery to mitigate or ameliorate the hypothermia condition. Topical application of the vasoconstrictor to the skin concentrates the vasoconstrictor effects in the skin,

and minimizes systemic effects of the vasoconstrictor. Optionally, application of one or more vasoconstrictors to the skin may be accompanied by application of heat from a source external to the patient.

[0060] As discussed in PCT2006, several applications of a vasoconstrictor may be needed in order to induce and maintain a high degree vasoconstriction (evidenced in visible skin blanching) for extended periods of time.

[0061] Synergetic combination formulas: In some embodiments, a combination of vasoconstrictors is used in order to obtain extended elevated vasoconstrictor effects. For example, some topical vasoconstrictors, such as epinephrine, initial act quickly (within about 20 minutes of application), but their activity diminishes significantly after 3 hours, whereas topical corticosteroids only begin to have significant vasoconstrictor effect about 7 hours after application, with lasting effects up to about 17 hours after application. Other vasoconstrictors, such as phenylephrine, when applied dermally, show intermediate periods of activity when applied topically, beginning to show their vasoconstricting effects after about 3 hours after application.

[0062] Therefore, in accordance with embodiments of the invention, the use of different combinations of vasoconstrictors, applied separately or in single formulation, can be conceived to address need of treatment for different lengths of time. For example, prevention or amelioration or minimization of hypothermia according to embodiments of the present invention can be fitted to different time scales depending on the planned duration of anesthesia associated with different known surgical operations.

[0063] Diosmin prolongs the vasoconstrictor effect of noradrenaline on the vein wall, increasing venous tone, and therefore reducing venous capacitance, distensibility, and stasis. Hence, a combination of vasoconstrictor agent and diosmin is provided in accordance with some embodiments of the invention.

[0064] As used herein, and as would be understood by the person of skill in the art, the recitation of a name of a compound is intended to include salts, solvates and inclusion complexes of that compound. Thus, in accordance with some embodiments of the invention, a compound as described herein, including in the contexts of pharmaceutical compositions, methods of treatment, and compounds *per se*, is provided as the salt form. Furthermore, when reference is made in a claim to a compound or a pharmaceutically acceptable salt thereof, it will be understood that claims which depend from that claim which refer to such a compound also include pharmaceutically acceptable salts of the compound, even if explicit reference is not made to the salts in the dependent claim.

[0065] Preventing associated high blood pressure. It will be appreciated that constriction of skin capillaries, e.g. as a result of topical vasoconstrictor application, may also result in undesired high blood pressure. In order to counteract this effect, in some embodiments of the present invention internal application (oral or intravenous) of a vasodilator is included. The vasodilator is preferably of a nitric-oxide donor type (e.g., nitroglycerine and derivatives) which primarily dilate internal, large blood vessels, and has relatively marginal effect on skin capillaries.

[0066] To minimize the potential influence of dermal application of vasoconstrictor on central blood pressure and heart rate, in some embodiments of the present invention the one or more vasoconstrictors are selective alpha agonist substances, such as phenylephrine or methoxamine.

[0067] Antiseptic combination. In the context of surgical operations, there is value to have the patient body skin surface as sterile as possible. Disinfection by topical alcohol swabs is common in patient preparation for surgery. Hence, in some embodiments of the present invention, the composition containing one or more vasoconstrictors further comprises a disinfecting agent, as known in the art.

[0068] Topical Administration. As stated, in some embodiments, topical dermal administration of vasoconstrictors is utilized; this minimizes systemic effects of the vasoconstrictors. Absorption through body outer surface skin is known to be less than via mucous membranes, e.g. via rectal, nasal or eye tissues. Hence, to achieve effective bioavailability of active vasoconstrictors, active vasoconstrictor concentration in the topical formulations will often need to be higher than 1%. The inclusion of a transdermal carrier and/or a skin penetration enhancer in such formulations may enable the concentration of the vasoconstrictors in the formulations to be reduced. Transdermal carriers and penetration enhancers known to those skilled in the art include polymethacrylic acid (PMA), carbopol, polyethylene glycol 8000 (PEG), propylene glycol (PG), water, alcohol, acetone, caprylic acid, caproic acid, oleic acid, lauric acid, isopropyl myristate, triethanolamine, or mixtures thereof. Transdermal penetration enhancers are also described, for example, in Karande et al., PNAS USA 102:4688-4693 (March 29, 2005). However, some of these may not be suitable for use on patients that have very sensitive skin or allergies. In some instances it may be desirable to include non-proteinaceous carriers, so as to form a liquid, particularly an aqueous liquid, or semi-solid or gel medium. Substances which may find use are physiologically acceptable substances, such as carbohydrates, polylactate, agaroses, dextrans, cellulose, gums, etc. Synthetic peptides may find use, such as polylysine, polyarginine, etc. The composition may be formulated with lipids to form liposomes or in a solid form in combination with silicones,

epoxide resins, hydroxyapatite, etc. The drugs and carrier will be selected to minimize any inactivating effects on the drugs.

[0069] The dermally administrable compositions used in accordance with embodiments of the invention include known pharmaceutical forms utilized for topical cutaneous administration, including solutions, gels, lotions, creams, ointments, foams, mousses, emulsions, microemulsions, milks, serums, aerosols, sprays, dispersions, microcapsules, vesicles and microparticles thereof. These compositions may be formulated according to techniques known in the art, or in accordance with techniques developed in the future.

[0070] The terms "pharmacologically acceptable carrier" and "dermatologically acceptable carrier", as used herein, mean that the carrier is suitable for cutaneous topical application, is compatible with the active agents any other components present in the pharmaceutical composition, and will not cause any untoward safety or toxicity concerns.

[0071] The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to, oil-in-water, water-in-oil, water-in-oil-in-water, and oil-in-water-in-silicon emulsions, are useful herein. As will be understood by the skilled artisan, a given component will distribute primarily into either the water or oil/silicon phase, depending on the water solubility/dispersibility of the component in the composition. A safe and effective amount of carrier is from about 50% to about 99.99%.

[0072] The composition, if desired, can contain excipients, binders, lubricants, disintegrants and the like, as is known in the art. If desired, it can also contain oily materials such as various fats, oils, waxes, hydrocarbons, fatty acids, higher alcohols, ester oils, metallic soaps, animal or vegetable extracts, hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic active agents; additional pharmaceutically effective components such as vitamins, hormones, amino acids; surfactants, colorants, dyes, pigments, fragrances, odor absorbers; antiseptics, preservatives, bactericides; humectants, thickeners, solvents, fillers; antioxidants; sequestering agents; sunscreens; or other known components and additives that do not unduly impair the vasoconstrictive effects of the vasoconstrictor. Additional descriptions of suitable compositions for topical dermal administration, and components suitable for inclusion therein, are described in Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co., 1990, and Remington: The Science and Practice of Pharmacy, 20th Edition, edited by A. Genaro, Lippincott Williams and Wilkins, Baltimore, MD, 2000.

[0073] Examples of suitable oils includes mineral oils, plant oils such as peanut oil, sesame oil, soybean oil, safflower oil, sunflower oil, animal oils such as lanolin or perhydrosqualene, synthetic oils such as purcellin oil, silicone oils such as cyclomethicome among others. Fatty

alcohols, fatty acids such as stearic acid and waxes such as paraffin wax, carnauba wax or beeswax may also be used as fats.

[0074] The composition may also contain emulsifying agents such as glyceryl stearate, solvents such as lower alcohols including ethanol, isopropanol, and propylene glycol, hydrophilic gelling agents including carboxyvinyl polymers or acrylic copolymers, polyacrylamides, polysaccharides, lipophilic gelling agents or fatty acid metal salts among others, hydrophilic acting agents such as amino acids, sugars, starch or urea, lipophilic active agents such as retinol or tocopherol.

[0075] In addition, the drug(s) can be employed encapsulated in liposomes or other controlled rate release compositions so as to provide for separate and distinct rates of release of the drug(s). Alternatively, other methods of encapsulation can be employed where one or more of the active ingredients are encapsulated in a biodegradable substance, where the rate of release is related to the thickness of the biodegradable coat.

[0076] The active ingredients used in accordance with embodiments of this invention may be uniformly dispersed in a physiologically acceptable medium, particularly aqueous, such as saline, phosphate buffered saline, distilled water, etc. The aqueous medium will be sufficient to provide for an amorphous dispersion, usually a solution, capable of flowing under mild pressure.

[0077] In addition to the vasoconstrictor(s) and optional thermogenics, a number of minor components may also be included for a variety of purposes. These agents will for the most part impart properties which protect the stability of the composition, control the pH, or the like. Illustrative agents include phosphate or acetate buffers, methyl or propyl paraben, polyethylene glycols, etc. These agents generally will be present in less than about 2 weight percent of the total composition, usually less than about 1 weight percent, and individually may vary from about 0.001 weight percent to about 1 weight percent.

[0078] In preparing the pharmaceutical formulations, other materials, as appropriate, may be added concomitantly or sequentially. After ensuring the uniform dispersion of the various components in the mixture, the mixture may be sterilized and sealed in an appropriate container. In the event the various components are unstable or form undesirable complexes when stored in a mixture prior to administration, each component may be dispensed at an appropriate concentration into a separate container for mixing just prior to administration. Those components which are stable together may be dispensed together into a single container for mixture with one or more reagents containing those additional ingredients found to promote instability or to form undesirable complexes. A device or kit containing separate components may be prepared which facilitates easy formulation prior to administration. The concentration of

each separate component is formulated so that the therapeutically effective concentration of each agent is achieved when all the separate components in the kit are admixed.

[0079] Combination with glove/sock peripheral warming devices. The use of external warming devices for selectively warming the palms and/or the feet of human subjects is particularly effective for warming of core body. Hence, in some embodiments, a glove shaped and/or sock shaped warming pad, optionally formed to be fitted over human hands and/or feet, respectively, may be utilized in conjunction with the dermal application of one or more vasoconstrictors. Such pads may contain heated gels or liquids or heat radiation sources as know in the art (e.g. warming pads, warming covers, warming bottles, and radiators). The control of such external heat sources is known in the art. In some embodiments, the at least one vasoconstrictor is applied topically to significant skin areas excluding the hands and/or feet, while the warming glove and sock devices are fitted and activated on the hands and/or feet respectively.

Example 1 - Epinephrine

[0080] The graphs in Fig. 1 summarize the results of experiments conducted on rats. Although there are differences between the thermoregulatory system of rats and humans, the tails and feet pads of rats function as thermoregulatory organs in a similar fashion to human skin. The rat tail skin and feet pads are exposed and not covered by fur. By controlling the blood flow to the tail skin and feet pads, the rat controls some of its heat dissipation to the environment. Only about 30% of the rat heat loss is regulated by the tail – much less than the role of the skin in humans.

[0081] Male Wistar rats, each about 400 g mass, were divided into three groups: a control group (C) of 8 rats, a test first group (A) of 7 rats, and a third test group (B) of 5 rats. All rats had test composition applied to the tail skin and the feet pads. All experiments were conducted at 23°C ambient room temperature. All groups went though an anesthesia period of one hour (t=0 is time of start of anesthesia), and a follow-up period of 3 hours after end of anesthesia. Core body temperature (CBT) and tail skin temperature of the rats was measured using a thermocouple-based digital thermometer with 0.1°C sensitivity.

[0082] Group C, the control group, was given a topical cream containing only base cream (similar to DermabaseTM oil-in-water emulsion base, Paddock Laboratories, Inc., Minneapolis, MN) with 10 wt.% penetration enhancer (propylene glycol), but no active vasoconstrictor. For test group A, the cream was identical to that used for the control group, except it contained 6 wt.% epinephrine, a vasoconstrictor. The cream for test group B was the same as that for group A, except that the cream contained 20 wt.% penetration enhancer.

[0083] The cream on both control group C and test group A was applied at two times: first, concomitantly with application of anesthesia (t=0), and again at 20 min into anesthesia (t = 20 m = 1/3 h). CBT and tail temperatures were measured at t = 0, 20, 40, 60, 120, 180 and 240 minutes.

[0084] Plot lines A and C in Fig. 1A show no significant difference in CBT between groups A and C for the first 40 minutes of the experiment, but thereafter show a full one degree difference is maintained between the CBT of the two groups through the remainder of the experiment. On the other hand, as shown in Fig. 1B, already 20 minutes into the experiment it was observed that the temperature of the tail was higher in the control group than in group A, due to decreased blood flow to the skin of the tails of the rats in group A due to vasoconstriction in the tail skin in this group. As application of the anesthetic was discontinued one hour into the experiment, at which point the rats were woken, these results indicate that the vasoconstrictor began to affect the blood vessels in the region to which the vasoconstrictor was applied soon after application, and that the effect of vasoconstrictor application on CBT lasted for at least 3 hours after anesthesia. The results also suggest that in some embodiments, it may be desirable to apply the vasoconstrictor to the skin of the patient 20 to 30 minutes prior to the administration of general anesthetic.

[0085] In test group (B), two changes were made to the experimental procedure. First, the concentration of penetration enhancer (propylene glycol) in the cream was doubled to 20 wt.%. Second, the time of first cream application was done at 30 min before anesthesia (t = -30 min) and the second cream application was given with initiation of administration of anesthetic (t = 0). The results, shown in the graphs, point to several effects. First, a core temperature difference between control group C and test group B is established already from the start of anesthesia at t = 0. Second, there is a stronger affect on CBT in group than in group A: there is a full 2°C different in CBT, established within 20 min from anesthesia, and maintained throughout the anesthesia time (t = 60 m). Third, there is a rapid fall-off the test group B temperature after 2 h. These results seem to indicate that the increased level of penetration enhancer caused a rapid discharge and absorption of the vasoconstrictor. In contrast, the lower level of penetration enhancer in test group A led to slower release of the vasoconstrictor, giving rise to longer and more stable duration of vasoconstrictor activity in the skin.

Example 2 – Norepinephrine Bitartrate

[0086] This experiment was similar to the experiment of Example 1, although Sprague Dawley albino rats were used. Also, the thermometer used was good for rectal measurements but less

fitting for skin measurements than the thermometer used in Example 1; hence, while the core temperature measurements are precise, the tail temperature measurements should be taken as indicative of relative effects but not absolute temperature. The test cream composition was 10% Norepinephrine vasoactive substance, 10% penetration enhancer (propylene glycol), and 80% conventional base cream.

[0087] All rats were subjected to one hour pre-anesthesia time (t= -60 to t=0), one hour anesthesia (t=0 to t=60), and 4 hours post anesthesia (t=60 to t=300). The appropriate cream was applied to the tail, feet, and ears skin surface of each rat. There were four rats in each test/control group. Vasoconstrictor cream was applied to the test group rats 3 times, at t = -60, t = -30, and t = 0 min before anesthesia. Core body temperature was measured rectally. Rat tail skin temperature was measured at around the mid-length of the tail by press touching the thermometer tip to the skin surface.

[0088] The results of the experiment are displayed graphically in Figs. 2A and 2B (black lines = test group, gray lines = control group). A difference in core body temperature can be observed starting about 20 min into anesthesia. The test group core body temperature is about 1-1.5°C higher than the control group core body temperature for the remaining anesthesia period and for 60 min post anesthesia.

[0089] It is also observed that at about 90 min post anesthesia, the control group temperature goes above the test group temperature, and that at the same time, the tail temperatures are also reversed. The higher/lower skin temperature is evidence for higher/lower degrees of vasodilatation. Thus, although it is not clear at present why this reversal effect is observed with norepinephrine, the results support the claimed method, in that the core temperature is affected by using topical vasoactive substances, where hypothermia during anesthesia is reduced by implementation of a vasoconstrictor action, and conversely hypothermia is increased by vasodilatation effect of topical substances to the skin.

[0090] From both the skin and core temperature we conclude that the topical skin Norepinephrine pronounced vasoconstrictor action (leading to cooler tail skin temperature) started about 80 min after the first application of cream, which is slower than the 20-30 min response time of the 6% Epinephrine cream used in Example 1.

[0091] Interestingly, according to the literature (Vetrivelan et al., Neural Plasticity **10**(4), 267-278 (2003)), injection of methoxamine, an α_1 adrenergic receptor agonist, into the preoptic area of adult male Wistar rat brains resulted in hypothermia.

[0092] Unless otherwise defined, all technical and scientific terms used herein have the same meanings as are commonly understood by one of ordinary skill in the art to which this invention

belongs. Although methods similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods are described herein.

[0093] All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the patent specification, including definitions, will prevail. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[0094] It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather the scope of the present invention is defined by the general combination of parts that perform the same functions as exemplified in the embodiments, and includes both combinations and sub-combinations of the various features described hereinabove as well as variations and modifications thereof, which would occur to persons skilled in the art upon reading the foregoing description.

WHAT IS CLAIMED IS:

1. A method for treating, preventing or delaying the onset of anesthetic hypothermia, which comprises applying to the skin of a patient who is under general anesthetic or is about to be put under general anesthetic an amount of at least one vasoconstrictor effective to treat, prevent or delay the onset of anesthetic hypothermia.

2. A method according to claim 1 wherein the at least one vasoconstrictor is present as a mixture of vasoconstrictors.

3. A method according to claim 1 or 2, where the at least one vasoconstrictor is present in a pharmaceutical composition.

4. A method according to claim 3, wherein the pharmaceutical composition is applied to at least 10% of the patient's skin.

5. A method according to claim 4, wherein the pharmaceutical composition is applied to at least 15% of the patient's skin.

6. A method according to claim 5, wherein the pharmaceutical composition is applied to at least 20% of the patient's skin.

7. A method according to claim 6, wherein the pharmaceutical composition is applied to at least 25% of the patient's skin.

8. A method according to claim 7, wherein the pharmaceutical composition is applied to at least 30% of the patient's skin.

9. A method according to claim 8, wherein the pharmaceutical composition is applied to at least 35% of the patient's skin.

10. A method according to claim 9, wherein the pharmaceutical composition is applied to at least 40% of the patient's skin.

11. A method according to claim 10, wherein the pharmaceutical composition is applied to at least 45% of the patient's skin.

12. A method according to claim 11, wherein the pharmaceutical composition is applied to at least 50% of the patient's skin.

13. A method according to any of claims 1 to 12, wherein the skin to which the at least one vasoconstrictor is applied includes skin selected from the group consisting of the palm of the hand, the sole of the foot, the ear, and the face.

14. A method according to any of claims 1 to 13, wherein the at least one vasoconstrictor is applied in the form of a dermally administrable pharmaceutical composition containing at least 1% by weight of the at least one vasoconstrictor.

15. A method according to claim 14, wherein the dermally administrable pharmaceutical composition contains at least 2% by weight of the at least one vasoconstrictor.

16. A method according to claim 15, wherein the dermally administrable pharmaceutical composition contains at least 3% by weight of the at least one vasoconstrictor.

17. A method according to claim 16, wherein the dermally administrable pharmaceutical composition contains at least 4% by weight of the at least one vasoconstrictor.

18. A method according to claim 17, wherein the dermally administrable pharmaceutical composition contains at least 5% by weight of the at least one vasoconstrictor.

19. A method according to claim 18, wherein the dermally administrable pharmaceutical composition contains at least 10% by weight of the at least one vasoconstrictor.

20. A method according to claim 19, wherein the dermally administrable pharmaceutical composition contains at least 15% by weight of the at least one vasoconstrictor.

21. A method according to claim 20, wherein the dermally administrable pharmaceutical composition contains at least 20% by weight of the at least one vasoconstrictor.

22. A method according to claim 21, wherein the dermally administrable pharmaceutical composition contains at least 25% by weight of the at least one vasoconstrictor.

23. A method according to claim 22, wherein the dermally administrable pharmaceutical composition contains at least 30% by weight of the at least one vasoconstrictor.

24. A method according to any of claims 1 to 23, wherein at least two vasoconstrictors are used, each of the at least two vasoconstrictors having peak effectiveness at different times after administration.

25. A method according to any of claims 1 to 24, wherein at least two vasoconstrictors are used, each of the at least two vasoconstrictors exerting its vasoconstrictive effect via a different mechanism.

26. A method according to any of claims 1 to 25, wherein at least two vasoconstrictors are used, each of the at least two vasoconstrictors having a different duration of effectiveness after administration.

27. A method according to any of claims 1 to 26, wherein the at least one vasoconstrictor is selected from the group consisting of (i) the group consisting of vasoactive agonists, vasopressor agents and vasoconstrictor drugs; (ii) an agent that acts on vasopressin receptors or adrenoreceptors; (iii) a calcium channel agonist; (iv) an agonist of the α_1 adrenergic receptor; (v) alfuzosin,doxazosin, epinephrine, methoxamine, naphazoline, norepinephrine, phenylephrine, prazosin, terazosin, tetrahydrozaline, tamsulosin; (vi) an agonist of the $5HT_1B_AD$ receptor; (vii) almotriptan, avitriptan, frovatriptan, oxidesumitriptan, rizatriptan, zolmitriptan; (viii)

chlorpheniramine, ethyinorephinephrine, mephenterine, metaraminol, oxymetazoline, oxymetazoline, phenylpropanolamine, potassium chloride, pseudoephidrine, propylhexadrine; (ix) ephedrine, angiotensin and vasopressin; (x) tetrahydrozoline HCl 0.05%, naphazoline HCl 0.03%, oxymetazoline HCl 0.025%; (xi) a vasoconstrictor extract selected from the group including ephedra sinica (ma huang), polygonum bistorta (bistort root), hamamelis virginiana (witch hazel), hydrastis canadensis (goldenseal), lycopus virginicus (bugleweed), aspidosperma quebracho (quebracho bianco), cytisus scoparius (scotch broom), guava extract, ellagic acid, caffeine, peppermint extract, chamomile oil, and cypress; (xii) an agent that positively affects the McKenzie vasoconstrictor assay; (xiii) topical corticosteroids, hydrocortisone, cortisol, synthetic corticosteroids, betametasone, fluticasone, mometasone; (xiv) antagonists of the β_2 adrenergic receptor.

28. A method according to any of claims 1 to 27, wherein the at least one vasoconstrictor or at least one vasoconstrictor in the mixture of vasoconstrictors is selected from the group consisting of methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, metaraminol, 4-NEMD, clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, xylazine, methyldopa, apraclonidine, brimonidine, detomidine, dexmedetomidine, lofexidine, romifidine, tizanidine, xylometazoline, amidephrine, amitraz, anisodamine, ergotamine, indanidine, medetomidine, mephentermine, midodrine, mivazerol, naphazoline, norfenefrine, octopamine, phenylpropanolamine, rilmenidine, synephrine, talipexole, tetrahydrozoline, xylometazoline, dobutamine, dopamine, denopamine, xamoterol, salbutamol, levosalbutamol, fenoterol, terbutaline, pirbuterol, procaterol, bitolterol, rimiterol, carbuterol, tulobuterol, reproterol, dopexamine, arformoterol, bambuterol, clenbuterol, formoterol, salmeterol, orciprenaline, metaproterenol, ritodrine, hexoprenaline, indacaterol, amibegron, solabegron, arbutamine, befunolol, isoxsuprine, nylidrin, oxyfedrine, prenalterol, ractopamine, bromoacetylalprenololmenthane, broxaterol, cimaterol, higenamine, mabuterol, methoxyphenamine, tretoquinol, zinterol isoprenaline, isoproterenol, epinephrine, norepinephrine, cirazoline, etilefrine, amphetamine, tyramine, ephedrine, pseudoephedrine, cocaine, allobarbital, amobarbital, aprobarbital, barbital, butobarbital, cyclobarbital, ethallobarbital, heptabarbital, hexobarbital, methohexital, pentobarbital, phenobarbital, proxibarbal, reposal, secobarbital, talbutal, thiopental, vinylbital, vinbarbital, brotizolam, cinolazepam, doxefazepam, estazolam, flunitrazepam, flurazepam, flutoprazepam, loprazolam, lormetazepam, nitrazepam, nimetazepam, midazolam, quazepam, temazepam, triazolam CL-218872, eszopiclone, indiplon, necopidem, pazinaclone, ROD-188, saripidem, suproclone, suriclone, SX-3228, U-89843A, U-90042, zaleplon, zolpidem, zopiclone, glutethimide,

methyprylon, pyrithyldione afloqualone, cloroqualone, diproqualone, etaqualone, mebroqualone, mecloqualone, methaqualone, methylmethaqualone acebrochol, allopregnanolone, alphadolone, alphaxolone, ganaxolone, hydroxydione, minaxolone, Org 20599, tetrahydrodeoxycorticosterone, dexmedetomidine, lofexidine, medetomidine, romifidine, tizanidine, xylazine agomelatine, melatonin, ramelteon, doxylamine, hydroxyzine, diphenhydramine, bromodiphenhydramine, carbinoxamine, orphenadrine, niaprazine, phenyltoloxamine, propiomazine, pyrilamine, scopolamine, aceburic acid, gamma-amino-beta-hydroxybutyric acid (GABOB), gamma-hydroxybutyric acid (GHB), sodium oxybate, Xyrem®, gamma-butyrolactone (GBL), 1,4-butanediol, 3-chloropropanoic acid, acetylglycinamide chloral hydrate, chloral hydrate, chloralodol, dichloralphenazone, paraldehyde, petrichloral, centalun, ethchlorvynol, ethinamate, hexapropymate, methylpentynol, meprobamate, carisoprodol, tybamate, methocarbamol, 2-methyl-2-butanol, acecarbromal, apronal, bromisoval, carbromal, clomethiazole, embutramide, etomidate, gaboxadol, loreclezole, mephenoxalone, sulfonmethane, trichloroethanol, triclofos, valerian, valnoctamide and trazadone.

29. A method according to any of claims 1 to 27, wherein the at least one vasoconstrictor is selected from the group consisting of α_1 agonists and β_2 blockers.

30. A method according to any of claims 1 to 27, wherein the at least one vasoconstrictor is selected from the group consisting of epinephrine, norepineohrine, and pharmaceutically acceptable salts thereof.

31. A method according to any of claims 1 to 30, wherein the at least one vasoconstrictor is applied in the form of a dermally administrable pharmaceutical composition that further comprises at least one of an antiseptic, antibiotic, antimycotic, or antiviral compound.

32. A method according to any of claims 1 to 31, wherein the at least one vasoconstrictor is applied in the form of a dermally administrable pharmaceutical composition that further comprises a penetration enhancer.

33. A method according to any of claims 1 to 32, wherein the at least one vasoconstrictor is applied in a concentration and to an amount of skin effective to raise the patient's core body temperature by at least 1°C for a period of at least 1 hour.

34. A method according to any of claims 1 to 33, wherein the at least one vasoconstrictor is applied in a concentration and to an amount of skin effective to raise the patient's core body temperature by at least 1°C within a period of 60 minutes from administration.

35. A method according to any of claims 1 to 34, wherein the at least one vasoconstrictor is applied in conjunction with at least one of (a) a penetration enhancer, (b) heat from an external source, and (c) a thermogenic substance.

36. A method according to any of claims 1 to 23 and 27 to 35, wherein one vasoconstrictor is used.

37. A method according to any of claims 1 to 35, wherein more than one vasoconstrictor is used.

38. A method according to claim 37, wherein a mixture of vasoconstrictors is used.

39. A kit comprising at least one vasoconstrictor and instructions or a label explaining how to use the at least one vasoconstrictor to treat, prevent or delay the onset of anesthetic hypothermia in a patient.

40. A kit according to claim 39, wherein the instructions or label instruct the user to apply the at least one vasoconstrictor to the skin of a patient who is under general anesthetic or is about to be put under general anesthetic in an amount effective to treat, prevent or delay the onset of anesthetic hypothermia.

41. A kit according to claim 39 or claim 40, wherein the at least one vasoconstrictor is present in a dermally acceptable pharmaceutical composition.

42. A kit according to claim 39 or 40, wherein the instructions or label instruct the user how to prepare a dermally administrable pharmaceutical composition containing the at least one vasoconstrictor.

43. A kit according to claim 41 or 42, wherein the dermally administrable pharmaceutical composition contains at least 1% by weight of the at least one vasoconstrictor.

44. A kit according to claim 43, wherein the dermally administrable pharmaceutical composition contains at least 2% by weight of the at least one vasoconstrictor.

45. A kit according to claim 44, wherein the dermally administrable pharmaceutical composition contains at least 3% by weight of the at least one vasoconstrictor.

46. A kit according to claim 45, wherein the dermally administrable pharmaceutical composition contains at least 4% by weight of the at least one vasoconstrictor.

47. A kit according to claim 46, wherein the dermally administrable pharmaceutical composition contains at least 5% by weight of the at least one vasoconstrictor.

48. A kit according to claim 47, wherein the dermally administrable pharmaceutical composition contains at least 10% by weight of the at least one vasoconstrictor.

49. A kit according to claim 48, wherein the dermally administrable pharmaceutical composition contains at least 15% by weight of the at least one vasoconstrictor.

50. A kit according to claim 49, wherein the dermally administrable pharmaceutical composition contains at least 20% by weight of the at least one vasoconstrictor.

51. A kit according to claim 50, wherein the dermally administrable pharmaceutical composition contains at least 25% by weight of the at least one vasoconstrictor.

52. A kit according to claim 51, wherein the dermally administrable pharmaceutical composition contains at least 30% by weight of the at least one vasoconstrictor.

53. A kit according to any of claims 41 to 52, wherein the instructions or label instruct the user to apply the pharmaceutical composition to at least 10% of the patient's skin.

54. A kit according to claim 53, wherein the instructions or label instruct the user to apply the pharmaceutical composition to at least 15% of the patient's skin.

55. A kit according to claim 54, wherein the instructions or label instruct the user to apply the pharmaceutical composition to at least 20% of the patient's skin.

56. A kit according to claim 55, wherein the instructions or label instruct the user to apply the pharmaceutical composition to at least 25% of the patient's skin.

57. A kit according to claim 56, wherein the instructions or label instruct the user to apply the pharmaceutical composition to at least 30% of the patient's skin.

58. A kit according to claim 57, wherein the instructions or label instruct the user to apply the pharmaceutical composition to at least 35% of the patient's skin.

59. A kit according to claim 58, wherein the instructions or label instruct the user to apply the pharmaceutical composition to at least 40% of the patient's skin.

60. A kit according to claim 59, wherein the instructions or label instruct the user to apply the pharmaceutical composition to at least 45% of the patient's skin.

61. A kit according to claim 60, wherein the instructions or label instruct the user to apply the pharmaceutical composition to at least 50% of the patient's skin.

62. A kit according to any of claims 39 to 61, wherein the instructions or label instruct that the skin to which the vasoconstrictor is applied includes skin selected from the group consisting of the palm of the hand, the sole of the foot, the ear, and the face.

63. A kit according to any of claims 39 to 62, wherein the kit comprises at least two vasoconstictors, each of the at least two vasoconstrictors having peak effectiveness at different times after administration.

64. A kit according to any of claims 39 to 63, wherein the kit comprises at least two vasoconstrictors, wherein each of the at least two vasoconstrictors exerts its vasoconstrictive effect via a different mechanism.

65. A kit according to any of claims 39 to 63, wherein the kit comprises at least two vasoconstrictors, wherein each of the at least two vasoconstrictors has a different duration of effectiveness after administration.

66. A kit according to any of claims 41 to 65, wherein the composition further comprises a a substance selected from the group consisting of a penetration enhancer, an antiseptic compound, an antibiotic compoud, an antimycotic compound, and an antiviral compound.

67. A kit according to any of claims 39 to 66, wherein at least one vasoconstrictor is selected from the group consisting of (i) the group consisting of vasoactive agonists, vasopressor agents and vasoconstrictor drugs; (ii) an agent that acts on vasopressin receptors or adrenoreceptors; (iii) a calcium channel agonist; (iv) an agonist of the α_1 adrenergic receptor; (v) alfuzosin,doxazosin, epinephrine, methoxamine, naphazoline, norepinephrine, phenylephrine, prazosin, terazosin, tetrahydrozaline, tamsulosin; (vi) an agonist of the $5HT_1B_AD$ receptor; (vii) almotriptan, avitriptan, frovatriptan, oxidesumitriptan, rizatriptan, zolmitriptan; (viii) chlorpheniramine, ethyinorephinephrine, mephenterine, metaraminol, oxymetazoline, oxymetazoline, phenylpropanolamine, potassium chloride, pseudoephidrine, propylhexadrine; (ix) ephedrine, angiotensin and vasopressin; (x) tetrahydrozoline HCl 0.05%, naphazoline HCl 0.03%, oxymetazoline HCl 0.025%; (xi) a vasoconstrictor extract selected from the group including ephedra sinica (ma huang), polygonum bistorta (bistort root), hamamelis virginiana (witch hazel), hydrastis canadensis (goldenseal), lycopus virginicus (bugleweed), aspidosperma quebracho (quebracho bianco), cytisus scoparius (scotch broom), guava extract, ellagic acid, caffeine, peppermint extract, chamomile oil, and cypress; (xii) an agent that positively affects the McKenzie vasoconstrictor assay; (xiii) topical corticosteroids, hydrocortisone, cortisol, synthetic corticosteroids, betametasone, fluticasone, mometasone; (xiv) antagonists of the β_2 adrenergic receptor.

68. A kit according to any of claims 39 to 66, wherein the at least one vasoconstrictor is selected from the group consisting of methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, metaraminol, 4-NEMD, clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, xylazine, methyldopa, apraclonidine, brimonidine, detomidine, dexmedetomidine, lofexidine, romifidine, tizanidine, xylometazoline, amidephrine, amitraz, anisodamine, ergotamine, indanidine, medetomidine, mephentermine, midodrine, mivazerol, naphazoline, norfenefrine, octopamine, phenylpropanolamine, rilmenidine, synephrine, talipexole, tetrahydrozoline, xylometazoline, dobutamine, dopamine, denopamine, xamoterol, salbutamol, levosalbutamol, fenoterol, terbutaline, pirbuterol, procaterol, bitolterol, rimiterol, carbuterol, tulobuterol, reproterol, dopexamine, arformoterol, bambuterol, clenbuterol, formoterol, salmeterol, orciprenaline, metaproterenol, ritodrine, hexoprenaline, indacaterol, amibegron, solabegron, arbutamine, befunolol, isoxsuprine, nylidrin, oxyfedrine, prenalterol, ractopamine, bromoacetylalprenololmenthane, broxaterol, cimaterol, higenamine, mabuterol,

methoxyphenamine, tretoquinol, zinterol isoprenaline, isoproterenol, epinephrine, norepinephrine, cirazoline, etilefrine, amphetamine, tyramine, ephedrine, pseudoephedrine, cocaine, allobarbital, amobarbital, aprobarbital, barbital, butobarbital, cyclobarbital, ethallobarbital, heptabarbital, hexobarbital, methohexital, pentobarbital, phenobarbital, proxibarbal, reposal, secobarbital, talbutal, thiopental, vinylbital, vinbarbital, brotizolam, cinolazepam, doxefazepam, estazolam, flunitrazepam, flurazepam, flutoprazepam, loprazolam, lormetazepam, nitrazepam, nimetazepam, midazolam, quazepam, temazepam, triazolam CL-218872, eszopiclone, indiplon, necopidem, pazinaclone, ROD-188, saripidem, suproclone, suriclone, SX-3228, U-89843A, U-90042, zaleplon, zolpidem, zopiclone, glutethimide, methyprylon, pyrithyldione afloqualone, cloroqualone, diproqualone, etaqualone, mebroqualone, mecloqualone, methaqualone, methylmethaqualone acebrochol, allopregnanolone, alphadolone, alphaxolone, ganaxolone, hydroxydione, minaxolone, Org 20599, tetrahydrodeoxycorticosterone, dexmedetomidine, lofexidine, medetomidine, romifidine, tizanidine, xylazine agomelatine, melatonin, ramelteon, doxylamine, hydroxyzine, diphenhydramine, bromodiphenhydramine, carbinoxamine, orphenadrine, niaprazine, phenyltoloxamine, propiomazine, pyrilamine, scopolamine, aceburic acid, gamma-amino-beta-hydroxybutyric acid (GABOB), gamma-hydroxybutyric acid (GHB), sodium oxybate, Xyrem®, gamma-butyrolactone (GBL), 1,4-butanediol, 3-chloropropanoic acid, acetylglycinamide chloral hydrate, chloral hydrate, chloralodol, dichloralphenazone, paraldehyde, petrichloral, centalun, ethchlorvynol, ethinamate, hexapropymate, methylpentynol, meprobamate, carisoprodol, tybamate, methocarbamol, 2-methyl-2-butanol, acecarbromal, apronal, bromisoval, carbromal, clomethiazole, embutramide, etomidate, gaboxadol, loreclezole, mephenoxalone, sulfonmethane, trichloroethanol, triclofos, valerian, valnoctamide and trazadone.

69. A kit according to any of claims 39 to 66, wherein the at least one vasoconstrictor is selected from the group consisting of α_1 agonists and β_2 blockers.

70. A kit according to any of claims 39 to 66, wherein the at least one vasoconstrictor is selected from the group consisting of epinephrine, norepinephrine, and pharmaceutically acceptable salts thereof.

71. A kit according to any of claims 39 to 70, wherein the instructions or label explain how to apply the at least one vasoconstrictor in a concentration and to an amount of skin effective to raise the patient's core body temperature by at least 1°C within a period of 60 minutes of administration.

72. A kit according to any of claims 39 to 70, wherein the instructions or label explain how to apply the at least one vasoconstrictor in a concentration and to an amount of skin effective to raise the patient's core body temperature by at least 1°C for a period of at least one hour.

73. A kit according to any of claims 39 to 72, wherein the instructions or label instruct the user to apply the at least one vasoconstrictor in conjunction with the dermal application of at least one of an antiseptic, antibiotic, an antimycotic or an antiviral compound.

74. A kit according to any of claims 39 to 73, wherein the kit further comprises at least one of an antibiotic, an antiseptic, antimycotic or an antiviral compound.

75. A kit according to any of claims 39 to 62 and 66 to 73, wherein the kit contains one vasoconstrictor.

76. A kit according to any of claims 39 to 73, wherein the kit contains more than one vasoconstrictor.

77. A kit according to claim 76, the kit contains a mixture of vasoconstrictors.

78. A method according to any of claims 1 to 38, wherein the at least one vasoconstrictor is selected from the group consisting of methoxamine, phenylephrine, 4-NEMD, clonidine, methyldopa, dobutamine, salbutamol, terbutaline, and isoprenaline.

79. A kit according to any of claims 39 to 77, wherein the at least one vasoconstrictor is selected from the group consisting of methoxamine, phenylephrine, 4-NEMD, clonidine, methyldopa, dobutamine, salbutamol, terbutaline, and isoprenaline.

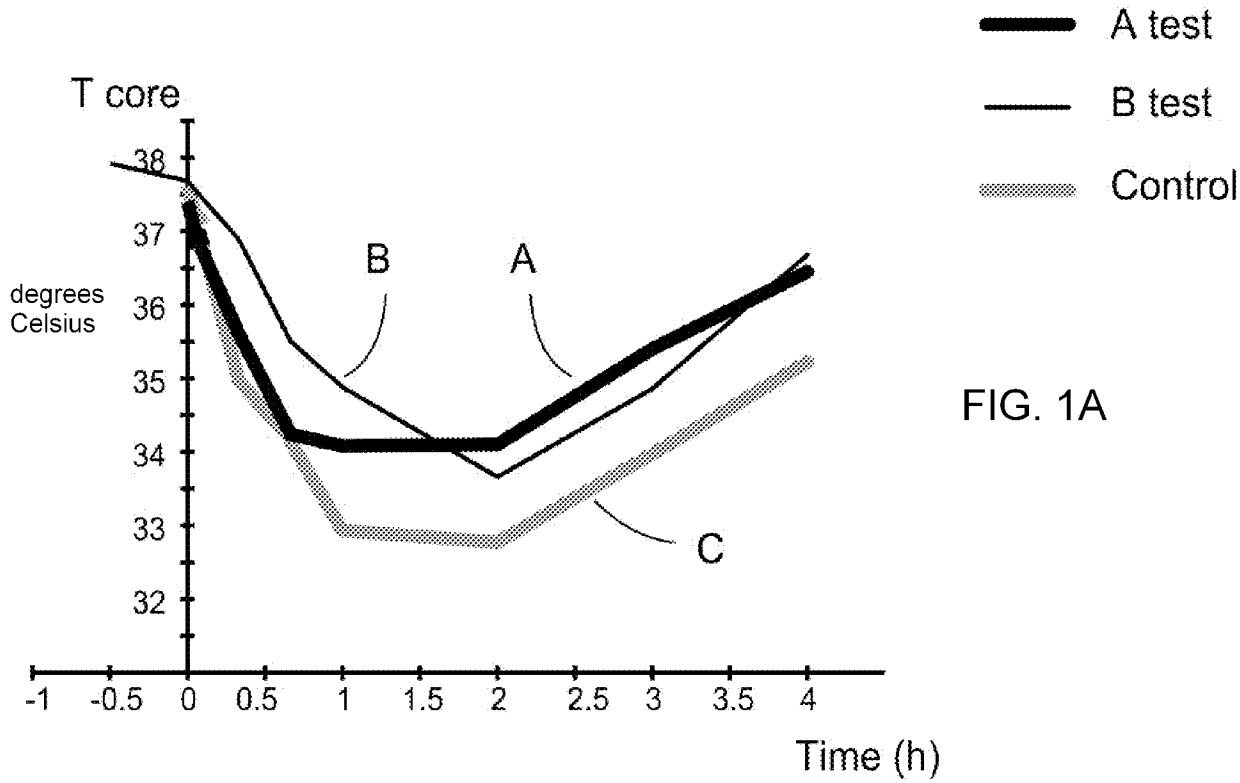

A test
B test
Control
T core
38
37
36
35
34
33
32
degrees Celsius
B
A
C
-1
-0.5
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (h)

FIG. 1A

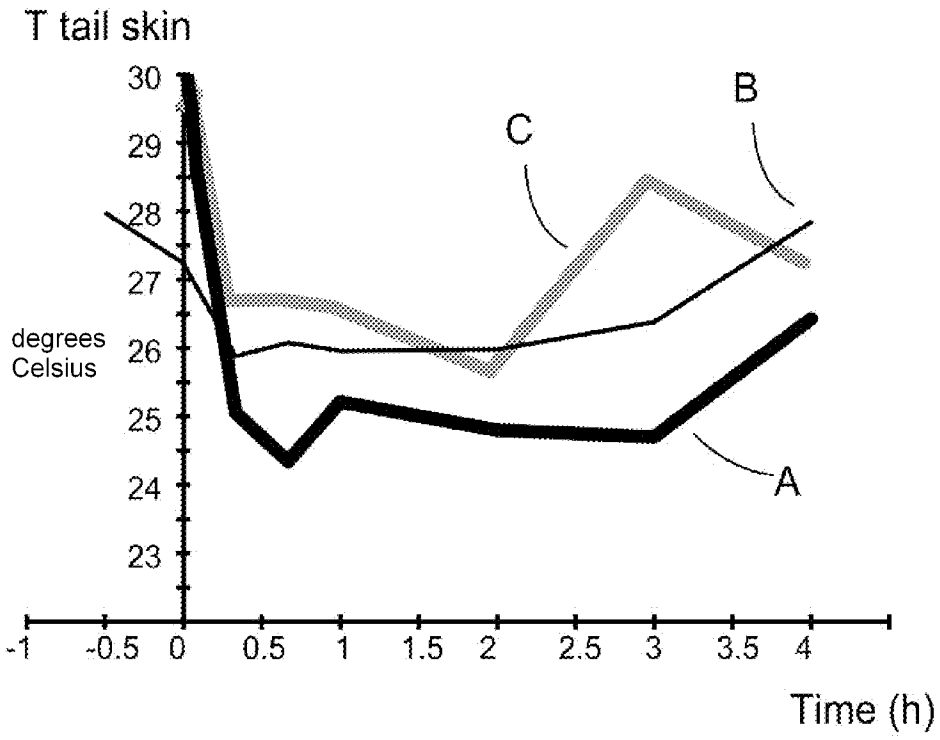
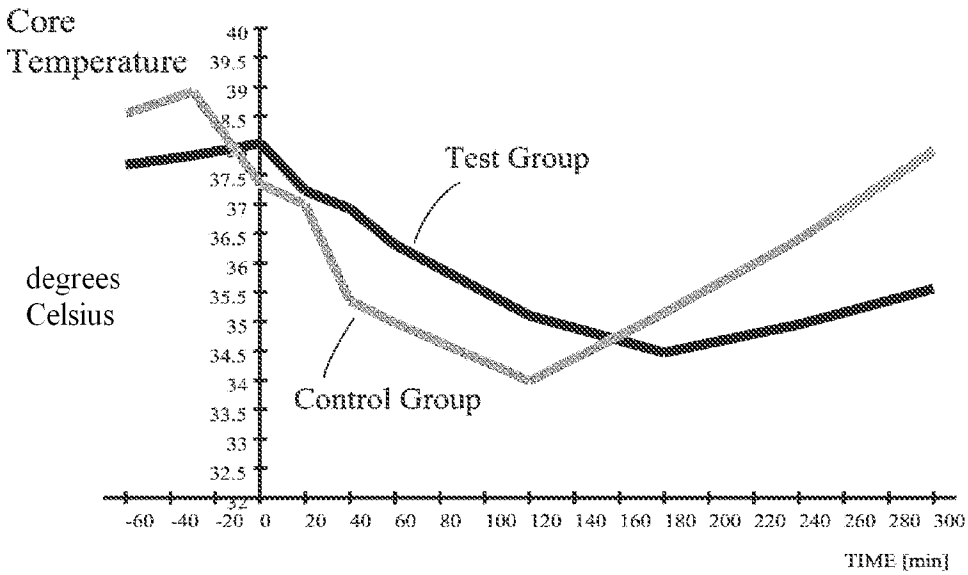

T tail skin
30
29
28
27
26
25
24
23
degrees Celsius
C
B
A
-1
-0.5
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (h)

FIG. 1B

FIG. 2A


Core
Temperature
40
39.5
39
37.5
37
36.5
36
35.5
35
34.5
34
33.5
33
32.5
Test Group
degrees
Celsius
Control Group
-60 -40 -20 0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300
TIME [min]

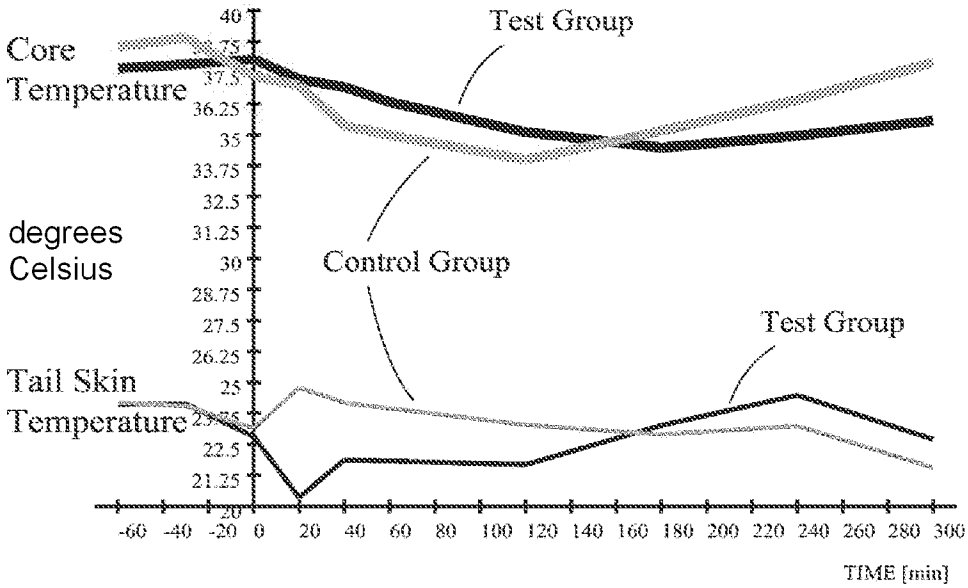

40
Test Group
Core
Temperature
37.5
36.25
35
33.75
32.5
31.25
30
28.75
27.5
26.25
25
22.5
21.25
20
degrees
Celsius
Control Group
Test Group
Tail Skin
Temperature
-60 -40 -20 0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300
TIME [min]

FIG. 2B