US 20150367090A1

(19) **United States**

(12) **Patent Application Publication**

Djupesland et al.

(10) **Pub. No.: US 2015/0367090 A1**

(43) **Pub. Date: Dec. 24, 2015**

(54) **NASAL ADMINISTRATION**

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(21) Appl. No.: **14/842,748**

(22) Filed: **Sep. 1, 2015**

Related U.S. Application Data

(63) Continuation of application No. 14/167,937, filed on Jan. 29, 2014, which is a continuation of application No. 12/161,466, filed on Feb. 1, 2011, filed as application No. PCT/GB2006/000182 on Jan. 19, 2006.

Publication Classification

(51) **Int. Cl.**

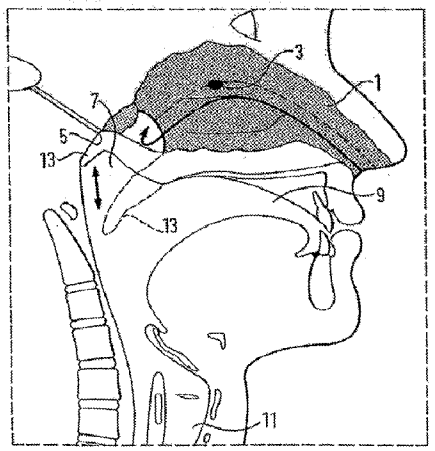
A61M 15/08	(2006.01)
A61M 16/20	(2006.01)
A61M 16/04	(2006.01)

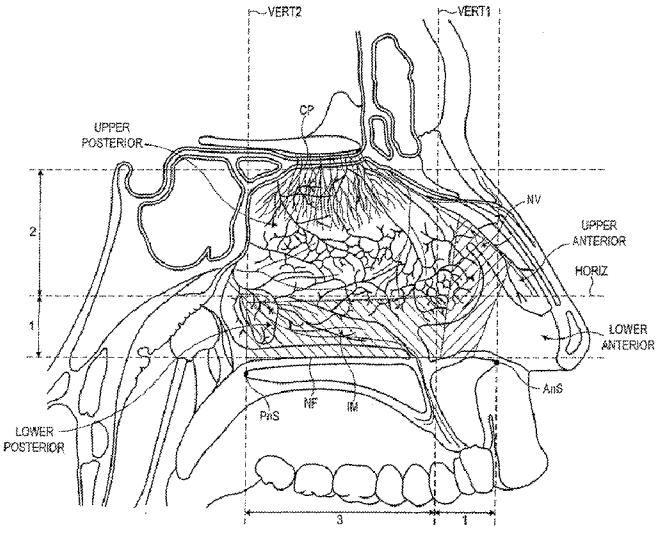
(52) **U.S. Cl.**

CPC ***A61M 15/08*** (2013.01); ***A61M 16/049*** (2014.02); ***A61M 16/20*** (2013.01); *A61M 2202/064* (2013.01)

(57) **ABSTRACT**

A delivery device for and method of providing for delivery of substance to the central nervous system (CNS) of a subject, the delivery device comprising: a nosepiece unit for insertion into a nasal airway of a subject and comprising an outlet unit which includes a nozzle for delivering substance into the nasal airway of the subject; and a substance supply unit which is operable to deliver a dose of substance to the nozzle; wherein the delivery device is configured such that at least 30% of the dose as initially deposited in the nasal airway is deposited in an upper posterior region of the nasal airway, thereby providing a CNS concentration of the substance, and hence CNS effect, which is significantly greater than that which would be predicted from a counterpart blood plasma concentration of the substance.





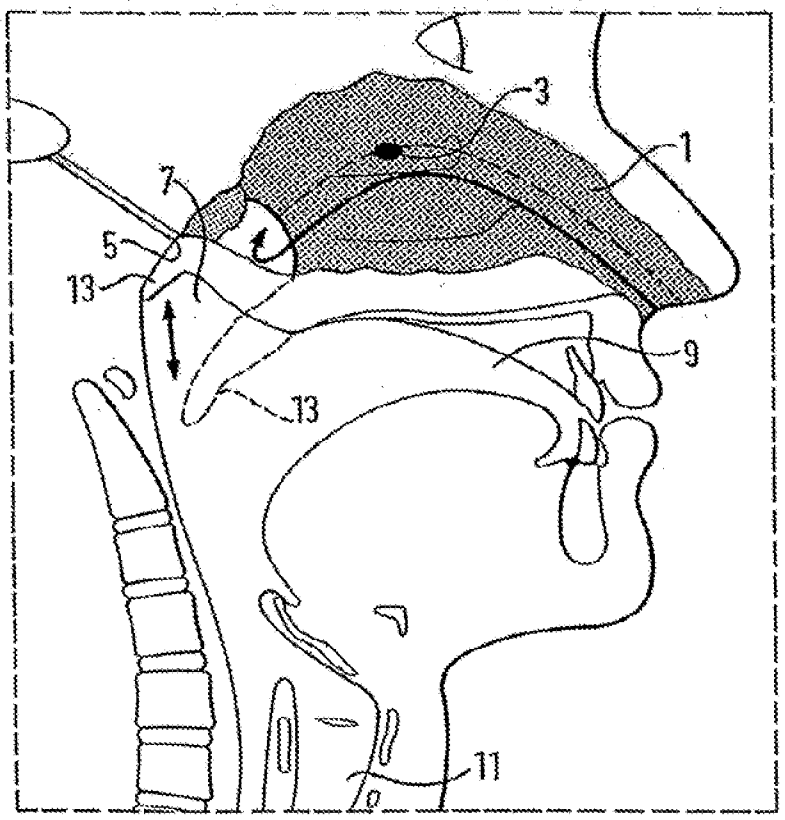


FIG. 1(a)

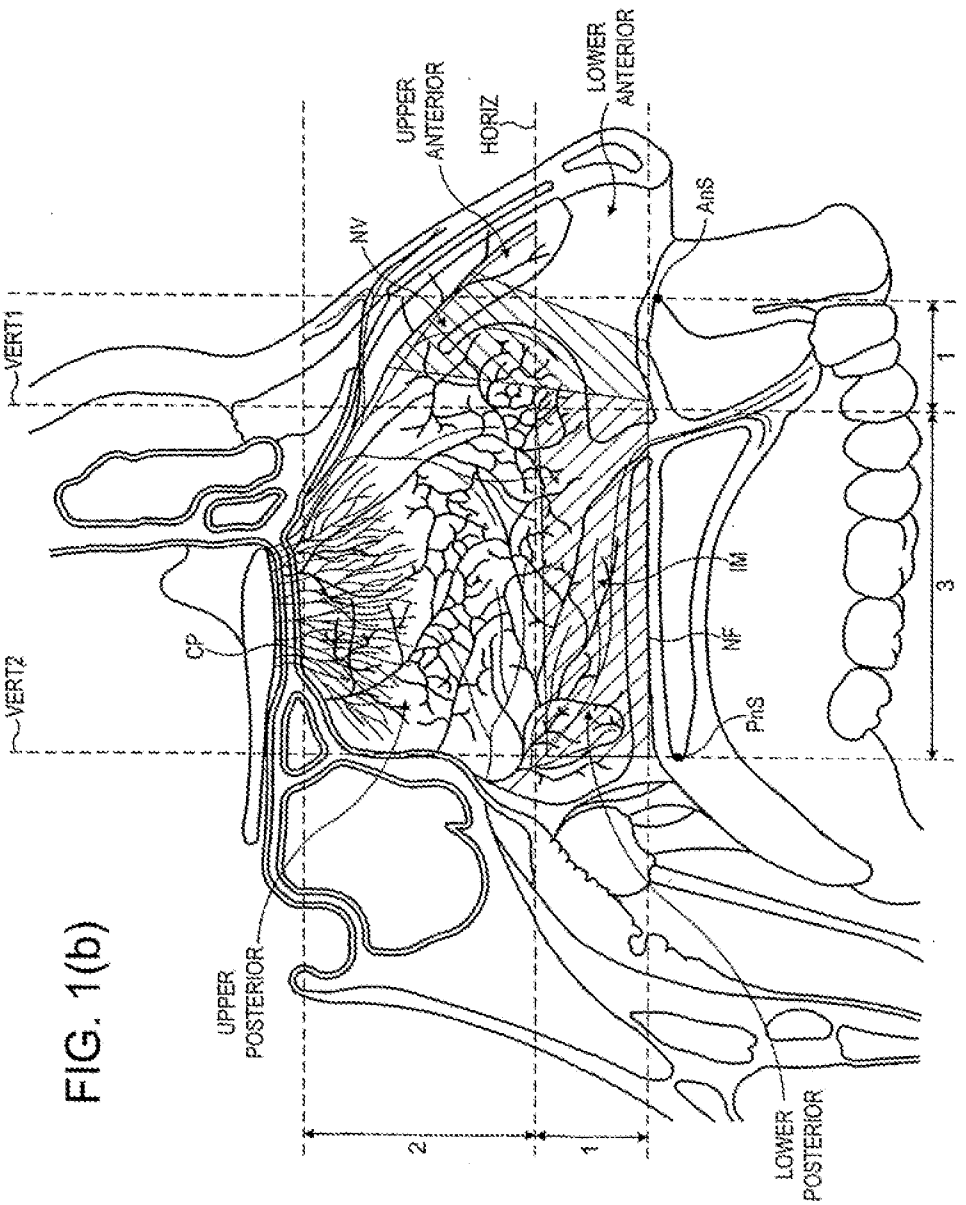

VERT1
VERT2
UPPER ANTERIOR
HORIZ
LOWER ANTERIOR
NV
AnS
CP
IM
MF
PnS
UPPER POSTERIOR
LOWER POSTERIOR
1
2
3

FIG. 1(b)

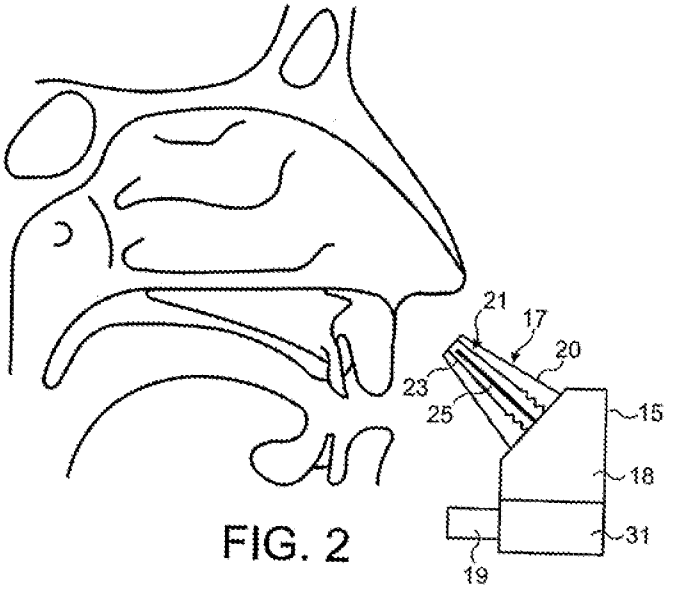


FIG. 2

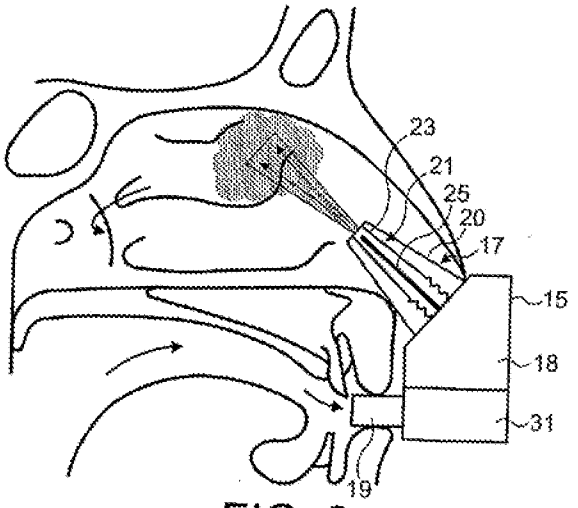


FIG. 3

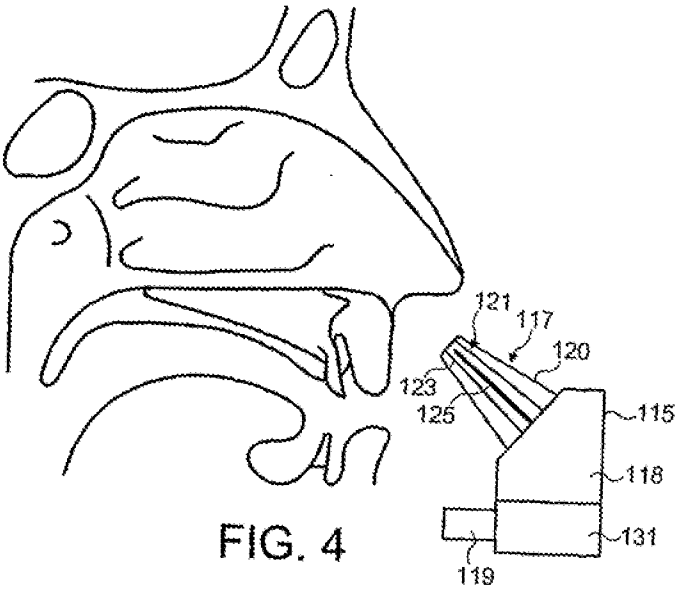

121
117
120
123
125
115
118
131
119

FIG. 4

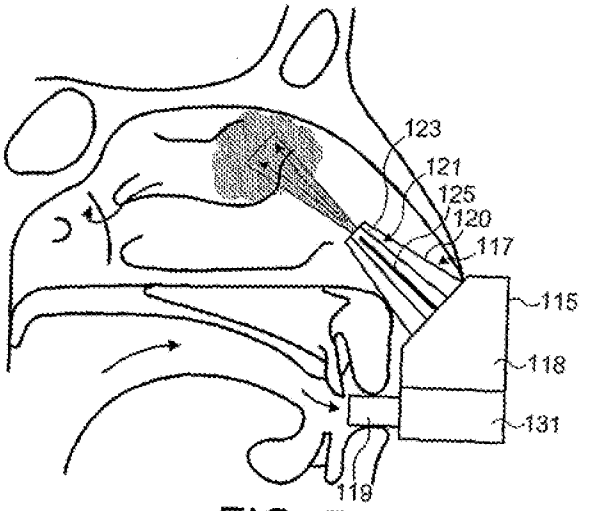

123
121
125
120
117
115
118
131
119

FIG. 5

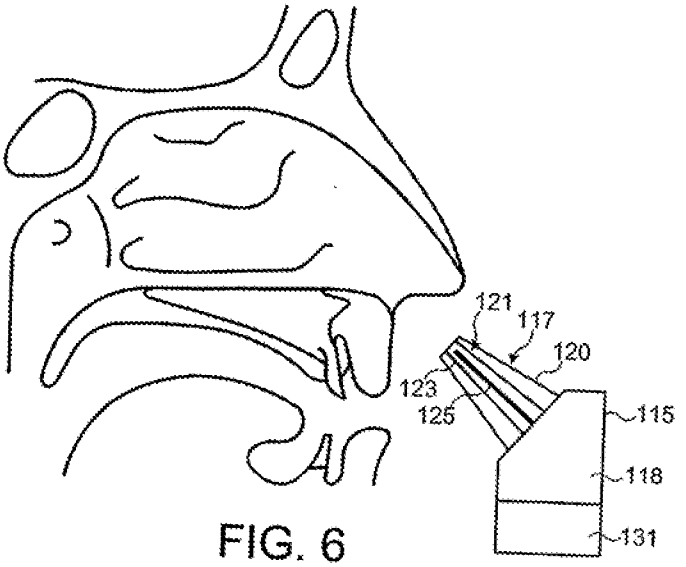


FIG. 6

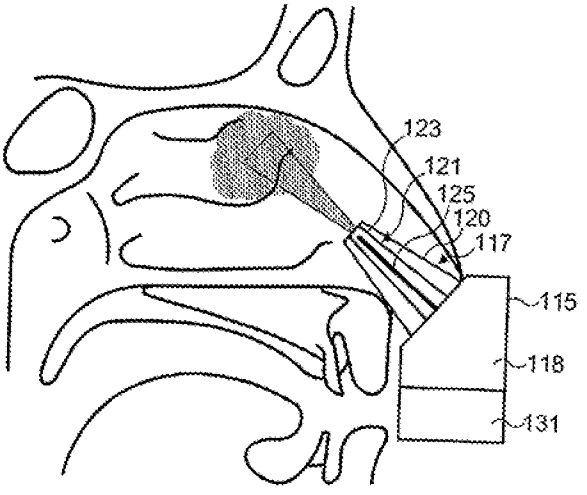


FIG. 7

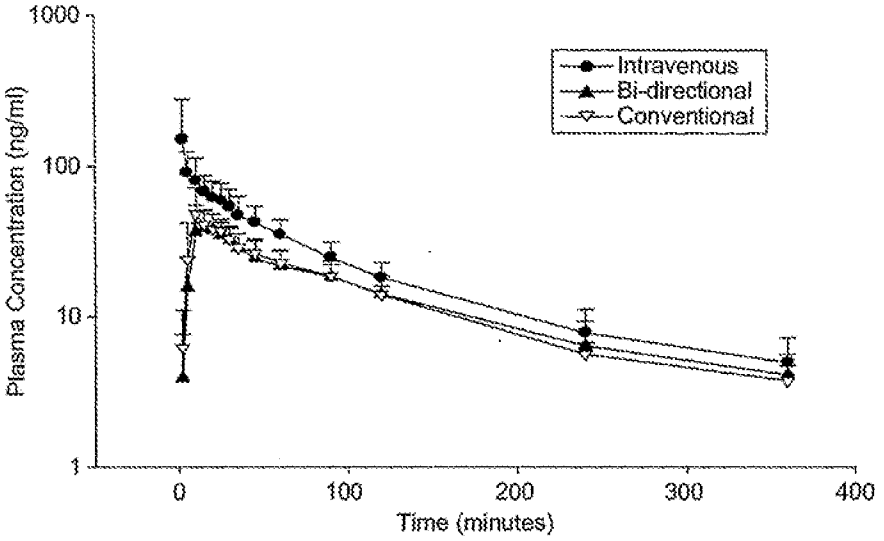

1000
100
10
1
Plasma Concentration (ng/ml)
0
100
200
300
400
Time (minutes)
Intravenous
Bi-directional
Conventional

FIG. 8

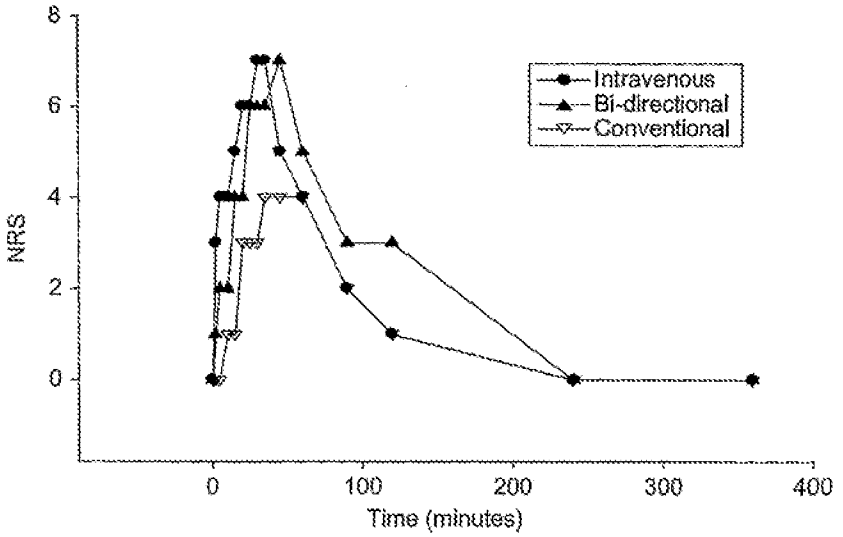

8
6
4
2
0
NRS
0
100
200
300
400
Time (minutes)
Intravenous
Bi-directional
Conventional

FIG. 9

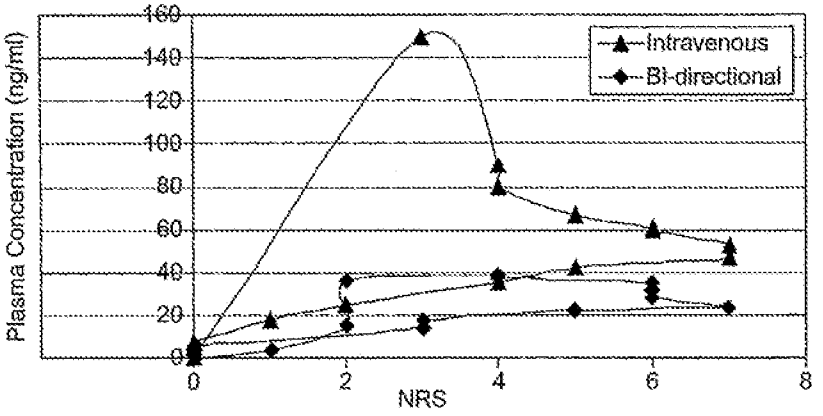

Plasma Concentration (ng/ml)
160
140
120
100
80
60
40
20
0
0
2
4
6
8
NRS
Intravenous
Bi-directional

FIG. 10

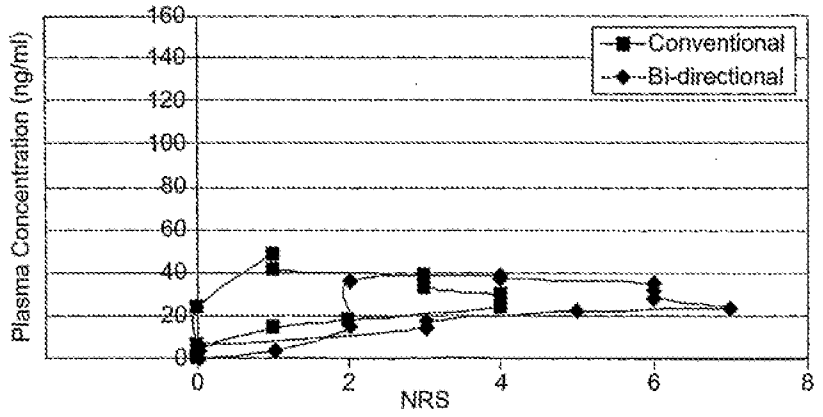

Plasma Concentration (ng/ml)
160
140
120
100
80
60
40
20
0
0
2
4
6
8
NRS
Conventional
Bi-directional

FIG. 11

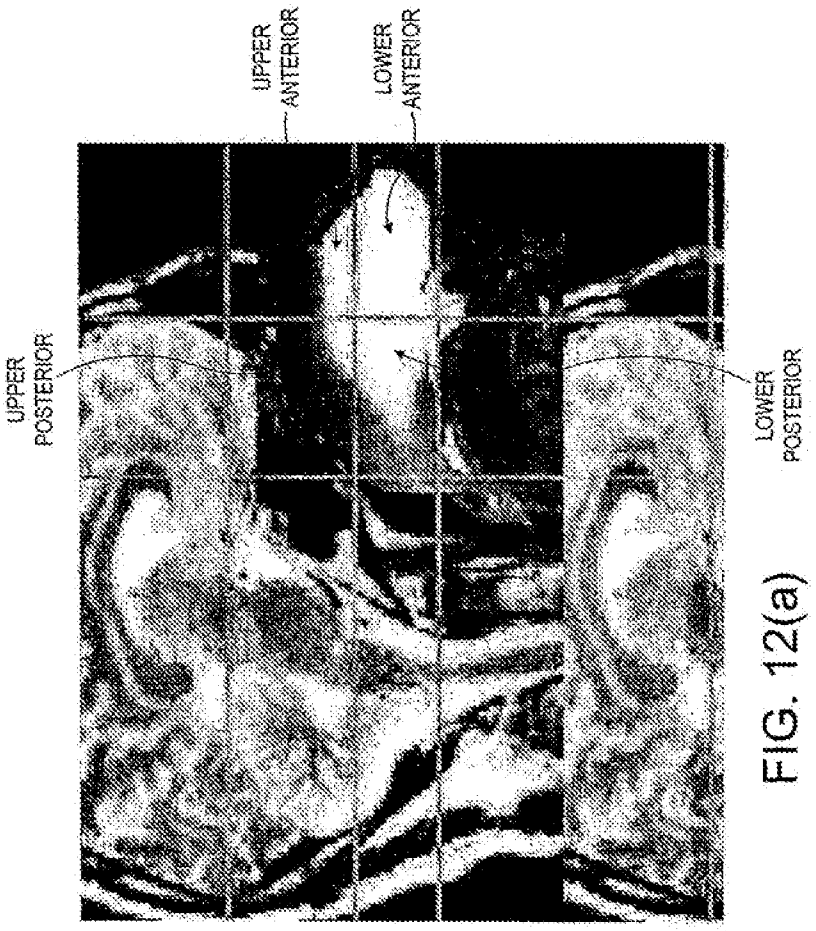

UPPER ANTERIOR
LOWER ANTERIOR
UPPER POSTERIOR
LOWER POSTERIOR

FIG. 12(a)

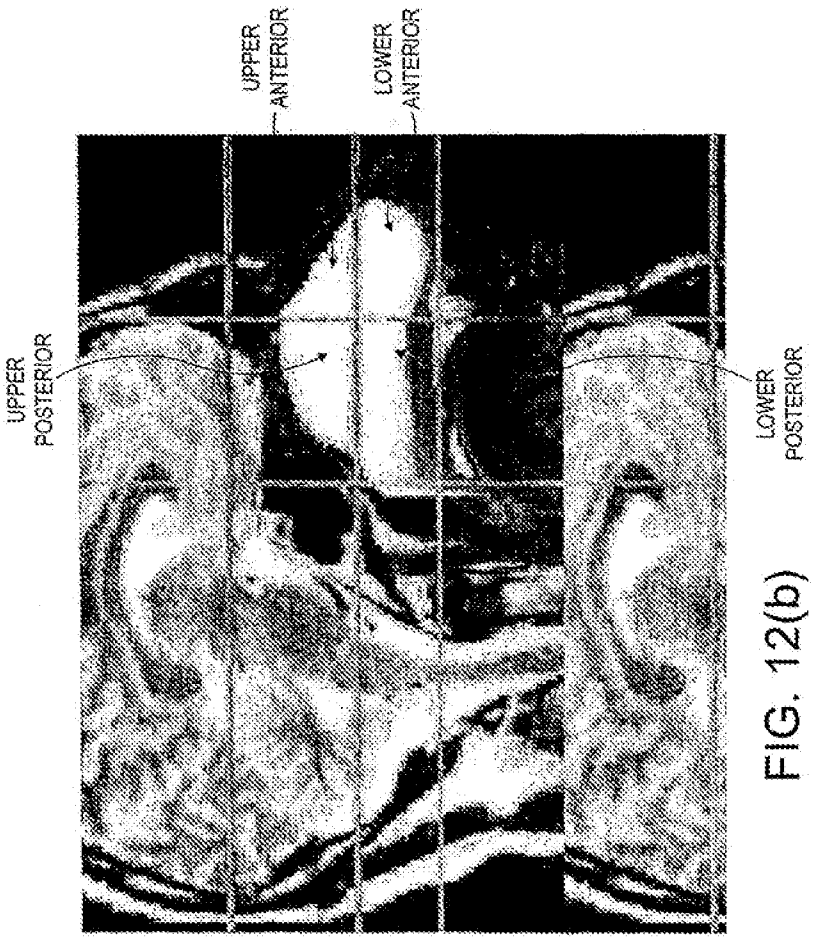

UPPER ANTERIOR
LOWER ANTERIOR
UPPER POSTERIOR
LOWER POSTERIOR

FIG. 12(b)

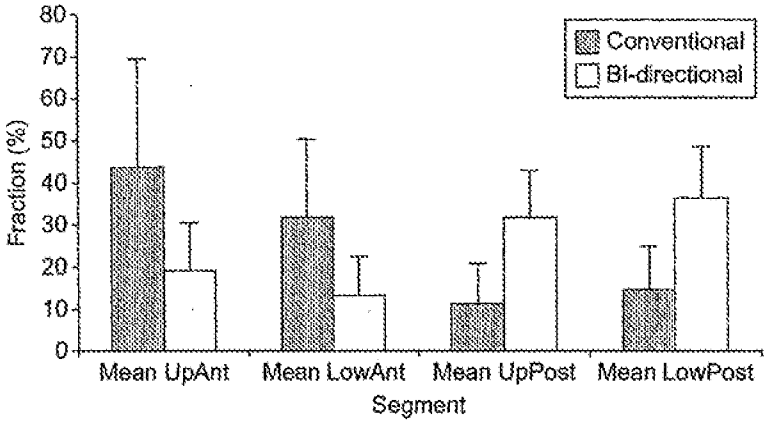

80
70
60
50
40
30
20
10
0
Fraction (%)
Conventional
Bi-directional
Mean UpAnt
Mean LowAnt
Mean UpPost
Mean LowPost
Segment

FIG. 13

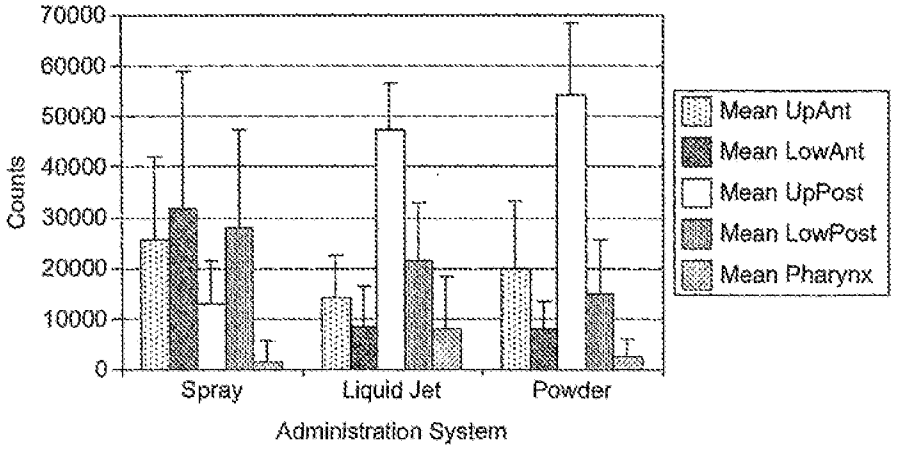

70000
60000
50000
40000
30000
20000
10000
0
Counts
Mean UpAnt
Mean LowAnt
Mean UpPost
Mean LowPost
Mean Pharynx
Spray
Liquid Jet
Powder
Administration System

FIG. 14

NASAL ADMINISTRATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation of U.S. patent application Ser. No. 2/161,466, filed on Feb. 1, 2011, which is a U.S. National phase application of PCT/GB2006/000182 filed Jan. 19, 2006, the disclosure of which applications are incorporated herein by reference.

FIELD OF INVENTION

[0002] The present invention relates to the nasal administration of substances, in particular drugs, to the central nervous system (CNS) via the nasal airway.

BACKGROUND

[0003] Referring to FIG. **1**(*a*), the nasal airway **1** comprises the two nasal cavities separated by the nasal septum, which airway **1** includes numerous ostia, such as the paranasal sinus ostia **3** and the tubal ostia **5**, and olfactory cells, and is lined by the nasal mucosa. The nasal airway **1** can communicate with the nasopharynx **7**, the oral cavity **9** and the lower airway **11**, with the nasal airway **1** being in selective communication with the anterior region of the nasopharynx **7** and the oral cavity **9** by opening and closing of the oropharyngeal velum **13**. The velum **13**, which is often referred to as the soft palate, is illustrated in solid line in the closed position, as achieved by providing a certain positive pressure in the oral cavity **9**, such as achieved on exhalation through the oral cavity **9**, and in dashed line in the open position.

[0004] In existing administration systems which provide for the administration of drugs to the CNS, which include pulmonary, parenteral, transdermal and oral administration systems, the concentration of drug that is attained within the CNS is mediated by the blood plasma concentration in the systemic, peripheral circulation. For many drugs, the concentration attainable within the CNS is much less than 10% of the blood plasma concentration.

[0005] Consequently, high blood plasma concentrations are required in order to achieve effective concentrations in the CNS. However, high blood plasma concentrations can cause unwanted effects, notably, systemic side effects. Thus, it is necessary to provide for a balance of the CNS efficacy against the peripheral side effect.

[0006] This may be particularly problematic in systems which require a rapid onset of action, as such systems rely on achieving high blood plasma concentrations in order to create a significant driving gradient for the rapid uptake of drug into the CNS.

[0007] Examples of drugs which exhibit systemic side effects include dopamine agonists, such as apomorphine and its derivatives and analogues, which can cause nausea as a side effect, triptans, such as sumatriptan and its derivatives and analogues, which can cause an angina-like side effect, vasopressin and desmopressin analogues which have activity on the learning pathway and can cause enuresis as a side effect, acetylcholinesterase inhibitors which can cause gastro-intestinal (GI) disorders as a side effect, and insulin which exhibits a reduced blood glucose level as a side effect.

[0008] It is one aim of the present invention to provide for the administration of substances, in particular drugs, at greater concentrations to the CNS for the same or reduced blood plasma concentrations, which has the benefit of at least reducing any peripheral side effects, which may be undesired. Such administration has particular benefit in relation to rescue situations.

[0009] It is another aim of the present invention to achieve a faster onset of action as compared to at least ones of the existing administration systems, and in particular existing nasal spray administration systems.

[0010] It is a further aim of the present invention to achieve a relatively rapid onset of action, but where avoiding the sharp peak plasma profiles associated with existing administration systems, such as in pulmonary, intravenous and transdermal systems.

SUMMARY OF THE INVENTION

[0011] The present inventors have recognized that an increased delivery of substance to the posterior region of the nasal airway, and in particular the upper posterior region of the nasal airway, as illustrated in FIG. **1**(*b*), relative to the anterior region of the nasal airway, surprisingly provides for a disproportionately greater CNS effect, which is suggestive of a greater uptake of substance into the CNS than would be predicted from the blood plasma concentration of the substance.

[0012] The posterior region of the nasal airway is that region which is posterior of the nasal valve NV, as illustrated in FIG. **1**(*b*). The nasal valve comprises the anterior bony cavum which contains inferior turbinate erectile tissue and septal erectile tissue, which are supported respectively by compliant ala tissue and the rigid cartilaginous septum (Mosby). These elements combine to form a dynamic valve, which extends over several millimetres, that adjusts nasal airflow, and is stabilized by cartilage and bone, modulated by voluntary muscle and regulated by erectile tissue. The lumen of the nasal valve is the section of narrowest cross-sectional area between the posterior and anterior regions of the nasal airway, and is much longer and narrower dorsally than ventrally, and this lumen defines a triangular entrance which extends to the piriform region of the bony cavum. The nasal valve is lined in its anterior part with transitional epithelium, with a gradual transition posterior to respiratory epithelium. The nasal valve and anterior vestibule define roughly the anterior one-third of the nose.

[0013] The posterior region of the nasal airway is that region which is lined with respiratory epithelium, which is ciliated, and olfactory epithelium, which comprises nerves which extend downwards through the cribiform plate CP from the olfactory bulb, whereas the anterior region of the nasal airway is that region which is lined with squamous epithelium, which is not ciliated, and transitional epithelium. The olfactory epithelium extends on both the lateral and medial sides of the nasal airway, and typically extends downwards about 1.5 to 2.5 cm.

[0014] The upper posterior region is the region above the inferior meatus IM, as illustrated in FIG. **1**(*b*), and encompasses the middle turbinate, the sinus ostia in infundibulum (ostia to maxillary, frontal and ethmoidal sinuses), the olfactory region, and the upper branches of the trigeminal nerve, and is that region which includes veins which drain to the venous sinuses that surround the brain.

[0015] As illustrated in FIG. **1**(*b*), the posterior region of the nasal airway is the nasal region posterior of an imaginary vertical plane VERT**1** which is located at a position corresponding to one-quarter of the distance between the anterior nasal spine AnS, which is a pointed projection at the anterior

extremity of the intermaxillary suture, and the posterior nasal spine PnS, which is the sharp posterior extremity of the nasal crest of the hard palate and represents the transition between the nose and the nasopharynx, which corresponds to a distance posterior of the anterior nasal spine AnS of between about 13 mm and about 14 mm (Rosenberger defines the distance between the anterior nasal spine AnS and the posterior nasal spine PnS as being 56 mm in eighteen year old boys and 53.3 mm in eighteen year old girls). As again illustrated in FIG. **1**(*b*), the posterior nasal region is bounded posteriorly by an imaginary vertical plane VERT**2** which extends through the posterior nasal spine PnS.

[0016] As further illustrated in FIG. **1**(*b*), the upper region of the nasal airway is an upper segment of the nasal airway which is bounded by the cribiform plate CP and a horizontal plane HORIZ which is located at a position corresponding to one-third of the distance between the nasal floor NF of the nasal airway and the cribiform plate CP, which corresponds to a height of typically between about 13 and about 19 mm above the nasal floor NF (Zacharek et al define the distance from the nasal floor NF to the cribiform plate CP as 46+/−4 mm).

[0017] The upper posterior region is thus that upper posterior region which is bounded by the above-defined vertical and horizontal planes VERT**1**, HORIZ.

[0018] The present inventors have postulated that this increased concentration within the CNS arises as a result of the veins in the upper posterior region of the nasal airway draining backwards to the venous sinuses that surround the brain, which leads to a higher local concentration in the cerebrovasculature. Although the sinus cavernous is outside the blood-to-brain barrier, animal models have shown that substances can be transported by a counter-current mechanism from the veins therein to the carotid artery which passes through the sinus cavernous. Other mechanisms have been proposed which include extra axonal transport along the surface of the olfactory and trigeminal nerves. This mode of transport is apparently quite rapid as compared to intra axonal transport.

[0019] The improved efficacy as achieved by the present invention as compared to existing nasal spray administration systems can apparently be explained in that such nasal spray administration systems have been determined to deliver largely to the anterior one-third of the nasal airway, that is, the nasal region anterior of the nasal valve, from which region drainage is mainly along the floor of the nose and in which region the veins drain to the external facial vein, which in turn drains to the external carotid and in turn to the peripheral circulation.

[0020] Recently, there has been a growing interest in alternative forms of drug administration, and in particular nasal administration. Nasal administration, with transmucosal absorption, can offer advantages, such as case of administration, rapid onset and patient control. Also, in bypassing gastrointestinal and hepatic pre-systemic elimination, nasal administration is applicable in nauseated and vomiting patients who may have problems in taking oral medication.

[0021] Several techniques and devices for intranasal drug administration have been developed. However, the use of manually-actuated spray pumps still dominates.

[0022] The present applicant has developed a novel nasal delivery system, as disclosed in WO-A-2000/051672, the content of which is herein incorporated by reference, which provides for the delivery of drugs and vaccines in a bi-directional air flow through the two nasal passages when connected in series by closure of the oropharyngeal velum.

[0023] In one embodiment this delivery system includes a mouthpiece through which the subject exhales, a nosepiece which is in fluid communication with the mouthpiece, and a spray pump which is actuated in response to exhalation through the mouthpiece to deliver an aerosol spray containing a substance from the nosepiece, such that an aerosol spray is delivered from the nosepiece together with an air flow which acts to entrain the delivered aerosol spray. In exhaling through the mouthpiece, the oropharyngeal velum closes the communication between the oral and nasal cavities to establish a bi-directional air flow which enters one nostril and exits the other nostril.

[0024] In one aspect the present invention provides a delivery device for providing for delivery of substance to the central nervous system (CNS) of a subject, the delivery device comprising: a nosepiece unit for insertion into a nasal cavity of a subject and comprising an outlet unit which includes a nozzle for delivering substance into the nasal cavity of the subject; and a substance supply unit which is operable to deliver a dose of substance to the nozzle; wherein the delivery device is configured such that at least 30% of the dose as initially deposited in the nasal cavity is deposited in an upper posterior region of the nasal cavity which is posterior of the nasal valve and above the inferior meatus, thereby providing a CNS concentration of the substance, and hence CNS effect, which is significantly greater than that which would be predicted from a counterpart blood plasma concentration of the substance.

[0025] In one embodiment the nozzle is configured to deliver an aerosol spray.

[0026] In one embodiment the aerosol spray is a liquid aerosol.

[0027] In another embodiment the aerosol spray is a powder aerosol.

[0028] In another embodiment the nozzle is configured to deliver a liquid jet.

[0029] In a further embodiment the nozzle is configured to deliver a powder jet.

[0030] In one embodiment the delivery device further comprises: a mouthpiece through which the subject in use exhales to cause closure of the oropharyngeal velum of the subject.

[0031] In one embodiment the outlet unit further comprises a delivery channel which is fluidly connected to the mouthpiece, whereby exhaled air from an exhalation breath of the subject is delivered through the nosepiece unit into the nasal cavity of the subject.

[0032] In another embodiment the outlet unit further comprises a delivery channel through which a gas flow, separate to an exhaled air flow from an exhalation breath of the subject, is in use delivered to the nasal cavity of the subject, and the delivery device further comprises: a gas supply unit for supplying a gas flow to the delivery channel.

[0033] In one embodiment the substance supply unit is breath actuated.

[0034] In another embodiment the substance supply unit is manually actuated.

[0035] Preferably, the delivery device is configured such that at least 40% of the dose as initially deposited in the nasal cavity is deposited in the upper posterior region of the nasal cavity.

[0036] More preferably, the delivery device is configured such that at least 50% of the dose as initially deposited in the nasal cavity is deposited in the upper posterior region of the nasal cavity.

[0037] In one embodiment the outlet unit further comprises a cuff member which acts to obstruct a region of the nasal cavity which is anterior of the nasal valve, such that substantially all of the delivered dose is delivered to a region of the nasal cavity which is posterior of the nasal valve.

[0038] In one embodiment the cuff member acts to close the nasal valve.

[0039] In another embodiment the outlet unit includes no cuff member which obstructs a region of the nasal cavity which is anterior of the nasal valve.

[0040] In one embodiment the region posterior of the nasal valve represents the posterior two-thirds of the nasal cavity and the region anterior of the nasal valve represents the anterior one-third of the nasal cavity.

[0041] In one embodiment the ratio of the peak CNS effect to the peak blood plasma concentration is at least 2 times that achieved using intravenous (IV) delivery.

[0042] Preferably, the ratio of the peak CNS effect to the peak blood plasma concentration is at least 3 times that achieved using intravenous (IV) delivery.

[0043] In another aspect the present invention provides a method of delivering substance to the central nervous system (CNS) of a subject, the method comprising the steps of: inserting a nosepiece unit into a nasal cavity of a subject, wherein the nosepiece unit comprises an outlet unit which includes a nozzle for delivering substance into the nasal cavity of the subject; and delivering a dose of substance to the nozzle; wherein at least 30% of the dose as initially deposited in the nasal cavity is deposited in an upper posterior region of the nasal airway which is posterior of the nasal valve and above the inferior meatus, thereby providing a CNS concentration of the substance, and hence CNS effect, which is significantly greater than that which would be predicted from a counterpart blood plasma concentration of the substance.

[0044] In one embodiment the nozzle is configured to deliver an aerosol spray.

[0045] In one embodiment the aerosol spray is a liquid aerosol.

[0046] In another embodiment the aerosol spray is a powder aerosol.

[0047] In another embodiment the nozzle is configured to deliver a liquid jet.

[0048] In a further embodiment the nozzle is configured to deliver a powder jet.

[0049] In one embodiment the method further comprises the step of: the subject exhaling through a mouthpiece to cause closure of the oropharyngeal velum of the subject.

[0050] In one embodiment the outlet unit is fluidly connected to the mouthpiece, whereby exhaled air from an exhalation breath of the subject is delivered through the nosepiece unit into the nasal cavity of the subject, such as to entrain the delivered substance.

[0051] In another embodiment a gas flow, separate to an exhaled air flow from an exhalation breath of the subject, is delivered to the nasal cavity of the subject, such as to entrain the delivered substance.

[0052] In one embodiment a dose of the substance is delivered in response to exhalation by the subject.

[0053] In another embodiment a dose of the substance is delivered in response to a manual operation by the subject.

[0054] Preferably, at least 40% of the dose as initially deposited in the nasal cavity is deposited in the upper posterior region of the nasal cavity.

[0055] More preferably, at least 50% of the dose as initially deposited in the nasal cavity is deposited in the upper posterior region of the nasal cavity.

[0056] In one embodiment the method further comprises the step of: obstructing a region of the nasal cavity which is anterior of the nasal valve, such that substantially all of the delivered dose is delivered to a region of the nasal cavity which is posterior of the nasal valve.

[0057] In one embodiment the obstructing step comprises the step of: closing the nasal valve.

[0058] In another embodiment a fluid communication remains between a region of the nasal cavity which is anterior of the nasal valve and a region of the nasal cavity which is posterior of the nasal valve.

[0059] In one embodiment the region posterior of the nasal valve represents the posterior two-thirds of the nasal cavity and the region anterior of the nasal valve represents the anterior one-third of the nasal cavity.

[0060] In one embodiment the ratio of the peak CNS effect to the peak blood plasma concentration is at least 2 times that achieved using intravenous (IV) delivery.

[0061] Preferably, the ratio of the peak CNS effect to the peak blood plasma concentration is at least 3 times that achieved using intravenous (IV) delivery.

[0062] In one embodiment the substance is a pharmaceutical drug.

[0063] In one embodiment the substance exhibits one or more systemic side effects.

[0064] In one embodiment the substance is a dopamine agonist.

[0065] Preferably, the substance comprises apomorphine or its pharmaceutically-acceptable derivatives or analogues.

[0066] In another embodiment the substance is a triptan.

[0067] Preferably, the substance comprises sumatriptan or its pharmaceutically-acceptable derivatives or analogues.

[0068] In a further embodiment the substance has activity on the learning pathway.

[0069] In one embodiment the substance comprises vasopressin or its pharmaceutically-acceptable derivatives or analogues.

[0070] In another embodiment the substance comprises desmopressin or its pharmaceutically-acceptable derivatives or analogues.

[0071] In a still further embodiment the substance is an acetylcholinesterase inhibitor.

[0072] Preferably, the substance comprises rivastigmine or its pharmaceutically-acceptable derivatives or analogues.

[0073] In one embodiment the substance is for the treatment of a condition which requires a rapid onset of action in order to ameliorate or abort a CNS event.

[0074] In one embodiment the substance is a benzodiazepine for the treatment of a panic disorder.

[0075] In another embodiment the substance is a triptan for the treatment of migraine.

[0076] In a further embodiment the substance is a gaba agonist for the treatment of neuropathic pain or to abort a partial or full epilepsy seizure.

[0077] In a still further embodiment the substance is insulin which is administered to regulate the satiety center.

[0078] In a yet further embodiment the substance is an insulin-like growth factor or its pharmaceutically-acceptable analogues which is administered to regulate the satiety center.

[0079] In yet another embodiment the substance is a peptide which is administered to regulate the satiety center.

[0080] In a still yet further embodiment the substance is a memory-enhancing agent which is administered prior to a learning episode.

[0081] In still yet another embodiment the substance is a sedative.

[0082] In one embodiment the substance is for the treatment of a panic disorder.

[0083] In another embodiment the substance is for the treatment of migraine.

[0084] In a further embodiment the substance is for the treatment of neuropathic pain.

[0085] In a still further embodiment the substance is for aborting a partial or full epilepsy seizure.

[0086] In yet another embodiment the substance is for regulating the satiety center.

[0087] In still yet another embodiment the substance is a memory-enhancing agent which is administered prior to a learning episode.

[0088] In a yet further embodiment the substance is for the treatment of a neurological disease, such as multiple sclerosis (MS), Alzheimer's disease or Parkinson's disease.

[0089] In still another embodiment the substance is for the treatment of sexual dysfunction.

[0090] In yet another embodiment the substance is a therapeutic vaccine, such as for the treatment of intracerebral tumours.

[0091] In a still further embodiment the substance is an angiotensin-converting enzyme (ACE) inhibitor, such as for the treatment of hypertension.

[0092] In a yet further embodiment the substance is for the treatment of insomnia.

[0093] In one embodiment the substance is a benzodiazepine.

[0094] In another embodiment the substance is a substance which acts on benzodiazepine receptors.

[0095] In a still further embodiment the substance is for the treatment of depression.

[0096] In one embodiment the substance is a selective serotonin re-uptake inhibitor.

[0097] In another embodiment the substance is a tricyclic anti-depressant.

[0098] In a yet further embodiment the substance is for the treatment of agrophobia.

[0099] In still another embodiment the substance is for the treatment of social anxiety disorder.

[0100] In still yet another embodiment the substance is for the treatment of obsessive compulsive disorder.

[0101] In yet still another embodiment the substance is for use in a treatment of smoking cessation.

[0102] In one embodiment the substance comprises nicotine.

[0103] In a still further embodiment the substance is a selective scrotonin re-uptake inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0104] The present invention will now be described hereinbelow by way of example only with reference to the accompanying drawings, in which:

[0105] FIG. **1**(*a*) schematically illustrates the anatomy of the upper respiratory tract of a human subject;

[0106] FIG. **1**(*b*) illustrates the segmentation of a nasal cavity in accordance with a preferred embodiment of the present invention;

[0107] FIG. **2** illustrates a nasal delivery device in accordance with a first embodiment of the present invention;

[0108] FIG. **3** illustrates the nasal delivery device of FIG. **2**, where operative in delivering substance to the nasal cavity of the subject;

[0109] FIG. **4** illustrates a nasal delivery device in accordance with a second embodiment of the present invention;

[0110] FIG. **5** illustrates the nasal delivery device of FIG. **4**, where operative in delivering substance to the nasal cavity of the subject;

[0111] FIG. **6** illustrates a nasal delivery device in accordance with a third embodiment of the present invention;

[0112] FIG. **7** illustrates the nasal delivery device of FIG. **6**, where operative in delivering substance to the nasal cavity of the subject;

[0113] FIG. **8** illustrates the time course for the measured blood plasma concentrations of midazolam for the three exemplified administration systems as employed in Example #1;

[0114] FIG. **9** illustrates the time course for the reported median sedation scores on a numeric rating scale (NRS) following administration of midazolam by the three exemplified administration systems as employed in Example #1;

[0115] FIG. **10** illustrates a plot of the reported median sedation scores as a function of the measured blood plasma concentration for the intravenous administration system and the bi-directional administration system as employed in Example #1;

[0116] FIG. **11** illustrates a plot of the reported median sedation scores as a function of the measured blood plasma concentration for the bi-directional administration system and the conventional nasal spray administration system as employed in Example #1;

[0117] FIG. **12**(*a*) illustrates the cumulative deposition as obtained by the conventional nasal spray administration system as employed in Example #2;

[0118] FIG. **12**(*b*) illustrates the cumulative deposition by obtained by the bi-directional administration system as employed in Example #2;

[0119] FIG. **13** graphically illustrates the mean deposition fractions in the four segmented nasal regions for both the conventional nasal spray administration system and the bi-directional administration system as employed in Example #2; and

[0120] FIG. **14** graphically illustrates the mean deposition fractions in the four segmented nasal regions for both the conventional nasal spray administration system and the bi-directional administration systems as employed in Example #3.

DETAILED DESCRIPTION OF THE INVENTION

[0121] FIGS. **2** and **3** illustrate a nasal delivery device in accordance with a first embodiment of the present invention.

[0122] The delivery device comprises a housing **15**, a nosepiece unit **17** for fitting in a nasal passage of a subject, a substance supply unit **18** for delivering substance to the nosepiece unit **17**, and a mouthpiece **19** through which the subject exhales to actuate the delivery device.

[0123] The nosepiece unit **17** comprises a nosepiece **20**, in this embodiment a frusto-conical element, for guiding the nosepiece unit **17** into a nasal passage of the subject and providing a fluid-tight seal with the nares of the nostril, and an outlet unit **21** for delivering substance, in this embodiment a CNS-active drug, to an upper posterior region of the nasal passage of the subject, in this embodiment an upper posterior region as bounded by a vertical plane which is located posterior of the anterior nasal spine AnS at a position corresponding to one-quarter of the distance between the anterior and posterior nasal spines AnS, PnS and a horizontal plane which is located above the nasal floor at a height one-third of the distance between the nasal floor and the cribiform plate. As discussed hereinabove, the present inventors have recognized that an increased delivery of substance to the upper posterior region of the nasal passage surprisingly provides for a disproportionately greater uptake of substance into the CNS than would be predicted from the blood plasma concentration of the substance.

[0124] In this embodiment the outlet unit **21** comprises a delivery channel **23** which is in fluid communication with the mouthpiece **19** such that an air flow is delivered into and through the nasal airway of the subject on exhalation by the subject through the mouthpiece **19**, and a nozzle **25** which is in fluid communication with the substance supply unit **18** and provides for delivery of substance into the nasal passage of the subject.

[0125] In this embodiment the substance supply unit **18** comprises a mechanical delivery pump, in particular a liquid delivery pump or a powder delivery pump, which delivers metered doses of substance, on actuation thereof.

[0126] In another alternative embodiment the substance supply unit **18** could comprise a dry powder delivery unit which delivers metered doses of a substance, as a dry powder, on actuation thereof. In one embodiment the substance supply unit **18** could provide for delivery of substance from a capsule.

[0127] In yet another alternative embodiment the substance supply unit **18** could comprise an aerosol canister which delivers metered volumes of a propellant, preferably a hydrofluoroalkane (HFA) propellant or the like, containing substance, either as a suspension or solution.

[0128] In yet another alternative embodiment the substance supply unit **18** could comprise a nebulizer which delivers metered doses of a substance, as an aerosol spray, on actuation thereof.

[0129] In this embodiment the nozzle **25** is configured to deliver a significant fraction of substance to the upper posterior region of the nasal passage, here an initial deposition of greater than 30% of the delivered dose.

[0130] In this embodiment the nozzle **25** is configured to deliver substance as an aerosol spray.

[0131] In an alternative embodiment the nozzle **25** could be configured to deliver substance as a jet, for example, as a column of liquid or powder. In delivering the substance as a jet, the substance can be more readily targeted at the upper posterior region of the nasal passage.

[0132] In this embodiment the substance supply unit **18** is a multi-dose unit for delivering a plurality of metered doses of the substance. In another embodiment the substance supply unit **18** could be a single-dose unit for delivering a single metered dose of the substance.

[0133] The substance supply unit **18** is pre-primeable, in this embodiment by loading a resilient element, and includes a breath-actuated release mechanism **31** which, when triggered, releases the resilient element and actuates the substance supply unit **18** to deliver a metered dose of the substance through the nozzle **25**.

[0134] In this embodiment the trigger mechanism **31** is configured to cause actuation of the substance supply unit **18** on generation of a predetermined pressure at the delivery channel **23**.

[0135] In an alternative embodiment the trigger mechanism **31** could be configured to cause actuation of the substance supply unit **18** on generation of a predetermined flow rate through the delivery channel **23**.

[0136] Operation of the delivery device will now be described hereinbelow with reference to FIG. **3** of the accompanying drawings.

[0137] The nosepiece unit **17** is first inserted into one of the nasal passages of a subject until the nosepiece **20** abuts the nares of the nostril such as to establish a fluid-tight seal therewith, at which point the distal end of the outlet unit **21** extends about 2 cm into the nasal passage of the subject, and the mouthpiece **19** is gripped in the lips of the subject.

[0138] The subject then begins to exhale through the mouthpiece **19**, which exhalation acts to close the oropharyngeal velum of the subject and drive an air flow through the delivery channel **23** of the outlet unit **21**, with the air flow passing into the one nasal passage, around the posterior margin of the nasal septum and out of the other nasal passage, thereby achieving a bi-directional air flow through the nasal airway of the subject.

[0139] In this embodiment, when the pressure developed at the delivery channel **23** reaches a predetermined value, the release mechanism **31** is triggered to actuate the substance supply unit **18** to deliver a metered dose of the substance to the nozzle **25** and into the nasal passage of the subject.

[0140] In an alternative embodiment the release mechanism **31** could be triggered in response to the generation of a predetermined flow rate through the delivery channel **23**.

[0141] In this embodiment, where the delivery device is a multi-dose device, the device is ready for further use following priming of the substance supply unit **18**.

[0142] FIGS. **4** and **5** illustrate a nasal delivery device in accordance with a second embodiment of the present invention.

[0143] The delivery device comprises a housing **115**, a nosepiece unit **117** for fitting in a nasal passage of a subject, a substance supply unit **118** for delivering substance to the nosepiece unit **117**, and a mouthpiece **119** through which the subject exhales to actuate the delivery device.

[0144] The nosepiece unit **117** comprises a nosepiece **120**, in this embodiment a frusto-conical element, for guiding the nosepiece unit **117** into a nasal passage of the subject and being configured both to provide a fluid-tight seal with the nares of the nostril and obstruct, in this embodiment close, the nasal passage at a position therealong, in this embodiment at a position corresponding substantially to the nasal valve, thereby obstructing the anterior one-third of the nasal passage and leaving open the posterior two-thirds of the nasal passage, as illustrated in FIG. **5**, and an outlet unit **121** for delivering substance, in this embodiment a CNS-active drug, to an upper posterior region of the nasal passage of the subject, in this embodiment an upper posterior region as bounded by a vertical plane which is located posterior of the anterior nasal spine AnS at a position corresponding to one-quarter of the distance between the anterior and posterior nasal spines

AnS, PnS and a horizontal plane which is located above the nasal floor at a height one-third of the distance between the nasal floor and the cribiform plate. As discussed hereinabove, the present inventors have recognized that an increased delivery of substance to the upper posterior region of the nasal passage surprisingly provides for a disproportionately greater uptake of substance into the CNS than would be predicted from the blood plasma concentration of the substance.

[0145] In this embodiment the outlet unit **121** comprises a delivery channel **123** which is in fluid communication with the mouthpiece **119** such that an air flow is delivered into and through the nasal airway of the subject on exhalation by the subject through the mouthpiece **119**, and a nozzle **125** which is in fluid communication with the substance supply unit **118** and provides for delivery of substance into the nasal passage of the subject.

[0146] In this embodiment the nosepiece **120** is formed of a substantially rigid material, but in other embodiments could be formed of a soft compressible and/or flexible material.

[0147] In this embodiment the substance supply unit **118** comprises a mechanical delivery pump, in particular a liquid delivery pump or a powder delivery pump, which delivers metered doses of substance, on actuation thereof.

[0148] In another alternative embodiment the substance supply unit **118** could comprise a dry powder delivery unit which delivers metered doses of substance, as a dry powder, on actuation thereof. In one embodiment the substance supply unit **118** could provide for delivery of substance from a capsule.

[0149] In yet another alternative embodiment the substance supply unit **118** could comprise an aerosol canister which delivers metered volumes of a propellant, preferably a hydrofluoroalkane (HFA) propellant or the like, containing substance, either as a suspension or solution.

[0150] In yet another alternative embodiment the substance supply unit **118** could comprise a nebulizer which delivers metered doses of substance, as an aerosol spray, on actuation thereof.

[0151] In this embodiment the nozzle **125** is configured to deliver substance as an aerosol spray.

[0152] In an alternative embodiment the nozzle **125** could be configured to deliver substance as a jet, for example, as a column of liquid or powder. In delivering the substance as a jet, the substance can be more readily targeted at the posterior region of the nasal passage.

[0153] In this embodiment the substance supply unit **118** is a multi-dose unit for delivering a plurality of metered doses of the substance. In another embodiment the substance supply unit **118** could be a single-dose unit for delivering a single metered dose of the substance.

[0154] The substance supply unit **118** is pre-primeable, in this embodiment by loading a resilient element, and includes a breath-actuated release mechanism **131** which, when triggered, releases the resilient element and actuates the substance supply unit **118** to deliver a metered dose of the substance through the nozzle **125**.

[0155] In this embodiment the trigger mechanism **131** is configured to cause actuation of the substance supply unit **118** on generation of a predetermined pressure at the delivery channel **123**.

[0156] In an alternative embodiment the trigger mechanism **131** could be configured to cause actuation of the substance supply unit **118** on generation of a predetermined flow rate through the delivery channel **123**.

[0157] Operation of the delivery device will now be described hereinbelow with reference to FIG. **5** of the accompanying drawings.

[0158] The nosepiece unit **117** is first inserted into one of the nasal passages of a subject until the nosepiece **120** abuts the nares of the nostril such as to establish a fluid-tight seal therewith, at which point the distal end of the nosepiece **120** extends about 2 cm into the nasal passage of the subject and closes the nasal valve, and the mouthpiece **119** is then gripped in the lips of the subject.

[0159] The subject then begins to exhale through the mouthpiece **119**, which exhalation acts to close the oropharyngeal velum of the subject and drive an air flow through the delivery channel **123** of the outlet unit **121**, with the air flow passing into the one nasal passage, around the posterior margin of the nasal septum and out of the other nasal passage, thereby achieving a bi-directional air flow through the nasal airway of the subject.

[0160] In this embodiment, when the pressure developed at the delivery channel **123** reaches a predetermined value, the release mechanism **131** is triggered to actuate the substance supply unit **118** to deliver a metered dose of the substance to the nozzle **125** and into the nasal passage of the subject.

[0161] In an alternative embodiment the release mechanism **131** could be triggered in response to the generation of a predetermined flow rate through the delivery channel **123**.

[0162] In this embodiment, where the delivery device is a multi-dose device, the device is ready for further use following priming of the substance supply unit **118**.

[0163] FIGS. **6** and **7** illustrate a nasal delivery device in accordance with a third embodiment of the present invention.

[0164] The delivery device of this embodiment is very similar to the delivery device of the above-described second embodiment, and thus, in order to avoid unnecessary duplication of description, only the differences will be described in detail, with like reference signs designating like parts.

[0165] The delivery device of this embodiment differs from that of the above-described second embodiment in omitting the mouthpiece **119** and the release mechanism **131** being manually actuated.

[0166] Operation of this delivery device is similar to that of the above-described second embodiment, except in that a bi-directional air flow is not generated through the nasal airway and the release mechanism **131** is actuated manually by the subject.

[0167] The present invention will now be described hereinbelow with reference to the following non-limiting Examples.

Example #1

[0168] The purpose of this study was to determine the relative sedative effect of midazolam where intranasally delivered using the novel, bi-directional administration system of the present applicant.

[0169] In this study, twelve healthy subjects, 4 male and 8 female, were studied. In separate sessions, the subjects received 3.4 mg of midazolam by one of three different administration systems, these being: an intravenous administration system in which a midazolam formulation was intravenously administered; conventional nasal spray administration system in which a midazolam formulation was conventionally nasally administered using a spray pump as supplied by Ing Erich Pfeiffer GmbH (Radolfsee, Germany) which is specified to generate a liquid spray with a mean

particle size of 43 μm, with 100 μl of the formulation being delivered to each nostril; and the bi-directional administration system of the first-described embodiment, and incorporating the same spray pump as the conventional nasal spray administration system, in which a midazolam formulation was nasally administered, with 100 μl of the formulation being delivered to each nostril.

[0170] Each study session was six hours in duration, and the sessions were separated by at least one week.

[0171] The intravenous formulation was a commercial midazolam HCl formulation (1 mg/ml (free base)) as supplied by Alpharma Inc (New Jersey, USA).

[0172] The nasal formulation was an aqueous solution containing midazolam base (1.7% w/v), sulfobutylether-β-cyclodextrin sodium salt with a molar substitution of 6.2 (Captisol®) (14% w/v) as supplied by CyDex Inc (Kansas, USA), hydroxypropyl methylcellulose (0.1% w/v), benzalkonium chloride (0.02% w/v), ethylene diaminetetraacetic acid (0.1% w/v) and phosphoric acid (0.73% w/v). The pH of the formulation was adjusted to a pH of between 4.20 and 4.35 with sodium hydroxide.

[0173] Venous blood samples, each having a volume of 9 ml, were drawn just prior to administration and at 2, 5, 10, 15, 20, 25, 30, 35, 45, 60, 90, 120, 240 and 360 minutes after administration, in order to allow for a determination of the blood plasma concentration of midazolam.

[0174] The blood plasma concentration of midazolam was determined according to Martens et al.

[0175] Samples, spiked with diazepam as an internal standard, were alkalised and extracted by toluene containing 0.1% w/v amyl alcohol. The resulting organic phase for each of the samples was then evaporated and the residue for each of the samples was derivatized with TBDMSTFA (/tert/-Butyldimethylsilyl)-/N/-methyltrifluoroacetamide with 1% w/v tert-butyldimethylsilyllchloride) at 60° C. After the excess of TBDMSTFA was evaporated, the residue for each of the samples was dissolved in ethyl acetate and analyzed in a gas chromatograph, in this embodiment an HP 5890 gas chromatograph equipped with an HP 5972 mass-spectrometry detector as supplied by Hewlett Packard Inc (USA). The midazolam and diazepam components were quantified by the mass ions 310 and 256, respectively.

[0176] FIG. **8** shows the time course for measured blood plasma concentrations of midazolam for the three different administration systems.

[0177] The curves for the two nasal administration systems are quite similar, whereas the curve for the intravenous administration system exhibits a blood plasma concentration which is always higher, although it has a parallel time-concentration curve to that of the nasal administration systems. These curves do not seem to be log-linear, indicating that a true elimination phase was not reached within the study session.

[0178] Table I below shows the pharmacokinetic characteristics of midazolam for the three administration systems.

[0179] In this study, the midazolam clearance, the volume of distribution, the elimination rate, the maximum plasma concentration Cmax, the time maximum plasma concentration Tmax, and the area under the curve AUC (linear trapezoidal rule) were calculated by computerized curve fitting using the Win-Nonlin Standard 4.1 as supplied by Pharsight Corporation (California, USA). The systemic clearance (Cl) =dose/AUC_{iv}, the apparent nasal clearances (Cl_n)=dose/AUC_n, and the respective bioavailabilities (F_x)=(AUC_x/$dose_y$)/(AUC_y/$dose_x$) were determined from the calculated values.

[0180] As can be seen, the two nasal administration systems exhibited similar pharmacokinetics, including a rapid mean T_{max} of 15/16 minutes. The intravenous administration system exhibited a shorter T_{max}, and a significantly larger area under the curve AUC. The bio-availabilities for the nasal administration systems were similar, in being 0.68 (0.57, 0.80) and 0.69 (0.57, 0.81) for the conventional spray administration system and the bi-directional spray administration system, respectively.

TABLE I

Administration System	T_{max} min	C_{max} ng/ml	$T_{1/2}$ min	AUClast min * ng/ml	AUCinf min * ng/ml	Vz#(obs) ml	Cl#(obs) ml/min
Intravenous	2.5	152	104	7349	8164	65378	451
	2; 3	73; 232	87; 121	5953; 8744	6486; 9842	54383; 76373	374; 527
Bi-directional	16	44	119	4615	5364	98551	589
	13; 19	34; 53	98; 139	3877; 5354	4476; 6252	64598; 132504	373; 805
Conventional	15	53	114	4628	5267	90691	551
	11; 18	39; 66	96; 133	4211; 5044	4792; 5742	59419; 12964	376; 726

#The calculations for the conventional nasal spray and bi-directional administration systems are not corrected for bio-availability.

[0181] In the results, the data is given as a median (min-max) or a mean (95% confidence interval (CI)). Regression analysis and ANOVA were used as appropriate. A bi-variate correlation (Pearson) was used to determine associations between variables. A paired sample t-test was used for group comparisons.

[0182] Subjective sedation was scored by a numeric rating scale (NRS) 0-10, where 0 is fully awake and 10 is falling asleep or as tired as you can imagine at 0, 2, 5, 10, 15, 20, 25, 30, 35, 45, 60, 90, 120 and 360 minutes after administration.

[0183] FIG. **9** represents the time course for subjective reporting of median sedation scores.

[0184] As can be seen, the bi-directional administration system achieved sedation scores which were equivalent to those of the intravenous administration system and yet unexpectedly had a much lower Cmax than that of the intravenous administration system. In addition, the bi-directional administration system has an onset of action which is considerably faster than the conventional nasal spray administration system and almost as fast as the intravenous administration system, and a markedly longer Tmax than the intravenous administration system.

[0185] FIG. **10** illustrates a plot of the reported median sedation scores as a function of blood plasma concentration for the intravenous administration system and the bi-directional administration system.

[0186] This plot clearly illustrates that the bi-directional administration system achieves the same peak CNS effect as the intravenous administration system, but with a substantially lower C_{max}. In this embodiment the ratio of peak CNS effect to C_{max} as achieved by the bi-directional administration system is about 3.5 times that achieved by intravenous administration.

[0187] FIG. **11** illustrates a plot of the reported median sedation scores as a function of blood plasma concentration for the bi-directional administration system and the conventional nasal spray administration system.

[0188] This plot clearly illustrates the marked effect as achieved by the bi-directional administration system as compared to the conventional nasal spray administration system, insofar as the bi-directional administration system achieves a substantially greater CNS effect than the conventional nasal spray administration system for a reduced C_{max}.

[0189] As discussed hereinabove, the present inventors have postulated that this increased concentration within the CNS arises as a result of the veins in the upper posterior region of the nasal passage draining backwards to the venous sinuses that surround the brain, which leads to a higher local concentration in the cerebrovasculature.

Example #2

[0190] This study provides for characterization of the deposition as achieved by the nasal administration systems of the above-described study.

[0191] In this study, nine healthy subjects, 4 females and 5 males, were studied.

[0192] In separate sessions, the subjects received a test solution by one of two different nasal administration systems, these corresponding to the nasal administration systems of the above study and being:

[0193] (i) a conventional nasal spray administration system in which a labeled test solution was conventionally nasally administered using a spray pump as supplied by Ing Erich Pfeiffer GmbH (Radolfsee, Germany) which is specified to generate a liquid spray with a mean particle size of 43 μm, with 100 μl of the test solution being delivered to one nostril; and

[0194] (ii) the bi-directional administration system of the first-described embodiment, and incorporating the same spray pump as the conventional nasal spray administration system, in which a labeled test solution was nasally administered, with 100 μl of the test solution being delivered to one nostril.

[0195] The two study sessions were performed two days apart to secure complete washout and decay.

[0196] The test solution was a ^{99m}Tc-DTPA solution, which was made by adding 120-150 MBq $^{99m}TcO_4^-$ (IF-ETEC generator) as supplied by Isopharma (Kjeller, Norway) in 6 ml of eluate to a vial containing freeze-dried diethylene triamine pentaacetic acid DTPA as supplied by Isopharma (Kjeller, Norway).

[0197] The deposition of the test solution in the nasal cavity was imaged using a scintillation camera system, here a VERTEX camera as supplied by ADAC Laboratories (USA) which was equipped with a low energy parallel hole high resolution VXGP collimator.

[0198] The aerosol was administered with the subjects sitting in the upright position, and, following administration, the subjects sat back such that the floor of the nasal cavity was projected at between 30 and 45 degrees with respect to the y-axis of the camera detector. This re-positioning took approximately 1 minute from the dose administration and imaging was initiated immediately thereafter. A total of 16 images, each containing 128×128 pixels, were acquired at two minute intervals. The subjects were instructed not to sniff during the imaging procedure.

[0199] As a consequence of the variation in administered activity, the acquired images were normalized so that the first image in each series, which represents the initial deposition, had a total image intensity equal to 100,000 within a region drawn around the nose as appearing in the cumulative images. As the floor of the nose and the curvature of the pharynx were clearly visible in the cumulative images as derived from each of the series, each series of images could conveniently be aligned.

[0200] Nasal dimensions were measured by acoustic rhinometry using Rhin2000 anatomic nose adaptors as supplied by RhinoMetrics (Lynge, Denmark), to verify normal nasal dimensions and to assist in nasal segmentation. Acoustic rhinometry identified the location of the minimal cross-sectional area corresponding to the head of the inferior turbinate (mean/SD: 2.3+/−0.25 cm), the head of the middle turbinate (mean/SD: 3.78+/−0.24 cm) and the transition to the epipharynx (mean/SD: 7.6+/−0.48 cm).

[0201] In order to allow for characterization of the deposition, the nose region was segmented into four rectangular nasal regions, namely, a lower anterior region (LowAnt), an upper anterior region (UpAnt), a lower posterior region (LowPost) and an upper posterior region (UpPost), and one pharyngeal region. The horizontal segmentation was fixed at a distance of 19 mm (4 pixels) from the nasal floor as determined from the most intense contour in the gradient image, and approximates the lower border of the middle turbinate. The vertical segmentation was fixed at a distance of 38 mm (8 pixels) anterior to the transition between the nose and nasopharynx, as visible in the cumulative images and lies between the nasal valve and head of the middle turbinate. Because of the limited spatial resolution of the camera system, the lower regions were extended caudally and the upper regions cranially, in order to include all counts originating from activity within the respective regions.

[0202] FIGS. **12**(*a*) and **12**(*b*) illustrate respectively the cumulative deposition as obtained by the two administration systems, with FIG. **12**(*a*) illustrating the cumulative deposition as obtained by the conventional nasal spray administration system and FIG. **12**(*b*) illustrating the cumulative deposition as obtained by the bi-directional administration system.

[0203] As will be clearly seen, the bi-directional administration system provides for a much greater fraction of the deposition to the upper posterior region as compared to the conventional nasal spray administration system.

[0204] Table II below shows the measured values for the initial deposition in the four nasal segments and the nasopharynx, as represented by the first in the series of images for each of the subjects.

[0205] Table II below shows the measured values for the initial deposition in the four nasal segments and the nasopharynx, as represented by the first in the series of images for each of the subjects.

TABLE II

Image	Conventional Mean	Conventional SD	Conventional CV	Conventional Nasal %	Conventional All %	Inventive Mean	Inventive SD	Inventive CV	Inventive Nasal %	Inventive All %	Difference P-value
Upper Anterior	32704	20205	0.62	43	38	12991	8095	0.62	19	17	$p < 0.02$
Lower Anterior	24172	14099	0.58	32	28	9228	6184	0.67	13	12	$p < 0.004$
Upper Posterior	8346	7242	0.87	11	10	22083	7599	0.34	32	28	$p < 0.004$
Lower Posterior	10983	7840	0.71	14	13	24997	8468	0.34	36	32	$p < 0.02$
Nasopharynx	8899	10469	1.18		10	8992	7871	0.88		11	NS
Sum Nasal Regions	76205	21448	0.28			69299	8635	0.12			NS
Sum All Regions	85104	14716	0.17			78290	8566	0.11			NS

[0206] FIG. **13** graphically illustrates the mean deposition fractions in the four segmented nasal regions for both the conventional nasal spray administration system and the bi-directional administration system.

[0207] As can be seen, the bi-directional administration system provides for initial deposition of 68% to the posterior nasal segments beyond the nasal valve of the total dose as deposited in the nasal cavity, whereas only 25% of the total dose as deposited in the nasal cavity is initially deposited in these segments following delivery with the conventional nasal spray administration system. In particular, following administration, the conventional nasal spray administration system provides for initial deposition of only 11% (SD 10%) of the total dose as deposited in the nasal cavity in the upper posterior region of the nasal cavity, whereas the bi-directional administration system provides for initial deposition of 32% (SD 11%) of the total dose as deposited in the nasal cavity in the upper posterior region of the nasal cavity.

[0208] The results of this study thus support the postulation of the present inventors that the increased concentration of the delivered substance to the CNS for any given blood plasma concentration could at least in part be a function of the relative fractions of substance which are delivered to the anterior and posterior regions of the nasal cavity, and in particular the upper posterior region.

Example #3

[0209] The purpose of this study was to characterize the deposition as achieved by powder aerosol and liquid jet administration systems in accordance with embodiments of the present invention.

[0210] In this study, nine healthy subjects, 4 females and 5 males, were studied.

[0211] In separate sessions, the subjects received a test substance by one of three different nasal administration systems, these being:

[0212] (i) a conventional nasal spray administration system in which a labeled test solution was conventionally nasally administered using a single-dose spray pump as supplied by Ing Erich Pfeiffer GmbH (Radolfsee, Germany) which is specified to generate a liquid spray with a mean particle size of 43 μm, with 100 μl of the test solution being delivered to one nostril;

[0213] (ii) the bi-directional administration system of the first-described embodiment where configured to deliver a labeled test powder from a conventional gelatine capsule, with approximately 4 mg of the test powder being nasally administered to one nostril; and

[0214] (iii) the bi-directional administration system of the first-described embodiment where incorporating the same single-dose spray pump as the conventional nasal spray administration system but with the nozzle modified, here truncated, to deliver a liquid jet, in which a labeled test solution was nasally administered, with 100 μl of the test solution being delivered to one nostril.

[0215] The three study sessions were performed two days apart to secure complete washout and decay.

[0216] The test solution was a ^{99m}Tc-DTPA solution, which was made by adding 120-150 MBq $^{99m}TcO_4^-$ (IFETEC generator) as supplied by Isopharma (Kjeller, Norway) in 6 ml of eluate to a vial containing freeze-dried diethylene triamine pentaacetic acid DTPA as supplied by Isopharma (Kjeller, Norway).

[0217] The test powder was a ^{99m}Tc-labelled powder as supplied by the Institute for Energy Technology (IFE) (Kjeller, Norway).

[0218] The deposition of the test solution and powder in the nasal cavity was imaged using a scintillation camera system, here a VERTEX camera as supplied by ADAC Laboratories (USA) which was equipped with a low energy parallel hole high resolution VXGP collimator.

[0219] The test samples were administered with the subjects sitting in the upright position, and, following administration, the subjects each turned their head to the side and positioned their cheek and the tip of their nose in an alignment device which was attached to the camera. In this study, the floor of the nasal cavity was projected close to the horizontal, corresponding to the x-axis of the camera detector. This repositioning took between approximately 10 and 30 seconds from the dose administration and imaging was initiated immediately thereafter. A total of 16 images, each containing 128×128 pixels, were acquired at two minute intervals. The subjects were instructed not to sniff during the imaging procedure.

[0220] As a consequence of the variation in administered activity, the acquired images were normalized so that the first image in each series, which represents the initial deposition, had a total image intensity equal to 100,000 within a region drawn around the nose as appearing in the cumulative images. As the floor of the nose and the curvature of the pharynx were

clearly visible in the cumulative images as derived from each of the series, each series of images could conveniently be aligned.

[0221] Nasal dimensions were measured by acoustic rhinometry using Rhin2000 anatomic nose adaptors as supplied by RhinoMetrics (Lynge, Denmark), to verify normal nasal dimensions and to assist in nasal segmentation.

[0222] In order to allow for characterization of the deposition, the nose region was segmented into four rectangular nasal regions, namely, a lower anterior region (LowAnt), an upper anterior region (UpAnt), a lower posterior region (LowPost) and an upper posterior region (UpPost), and one pharyngeal region. The horizontal segmentation was fixed at a distance of approximately 19 mm (4 pixels) from the nasal floor as determined from the most intense contour in the gradient image, and approximates the lower border of the middle turbinate. The vertical segmentation was fixed at a distance of approximately 38 mm (8 pixels) anterior to the transition between the nose and nasopharynx, as visible in the cumulative images and lies between the nasal valve and head of the middle turbinate. Because of the limited spatial resolution of the camera system, the lower regions were extended caudally and the upper regions cranially, in order to include all counts originating from activity within the respective regions.

[0223] Tables III(a) to (c) below show the measured values for the initial deposition in the four nasal segments and the nasopharynx, as represented by the first in the series of images for each of the subjects, for each of the administration systems.

TABLE III(a)

Image	Conventional Mean	Conventional SD	Conventional CV	Conventional Nasal %	Conventional All %
Upper Anterior	25565	16531	0.65	26	26
Lower Anterior	31935	26981	0.84	33	32
Upper Posterior	12893	8377	0.65	13	13
Lower Posterior	27999	19622	0.70	28	28
Nasopharynx	1579	4293	2.72		1
Sum Nasal Regions	98392				
Sum All Regions	99971				

TABLE III(b)

Image	Liquid Jet Mean	Liquid Jet SD	Liquid Jet CV	Liquid Jet Nasal %	Liquid Jet All %
Upper Anterior	13993	8493	0.61	15	14
Lower Anterior	8409	7893	0.94	9	8
Upper Posterior	47518	9150	0.19	52	48
Lower Posterior	21598	11179	0.52	24	22
Nasopharynx	8105	10310	1.27		8
Sum Nasal Regions	91518				
Sum All Regions	99623				

TABLE III(c)

Image	Powder Mean	Powder SD	Powder CV	Powder Nasal %	Powder All %
Upper Anterior	20019	13147	0.66	21	20
Lower Anterior	8115	5445	0.67	8	8
Upper Posterior	54281	14196	0.26	56	54
Lower Posterior	14917	10682	0.72	15	15
Nasopharynx	2515	3501	1.39		3
Sum Nasal Regions	97332				
Sum All Regions	99847				

[0224] FIG. **14** graphically illustrates the mean deposition fractions in the four segmented nasal regions for both the conventional nasal spray administration system and the bi-directional administration systems.

[0225] As can be seen, the bi-directional liquid jet administration system provides for initial deposition of 76% of the dose as initially deposited in the nasal cavity to the posterior segments beyond the nasal valve and the powder administration system provides for initial deposition of 71% of the dose as initially deposited in the nasal cavity to the posterior segments beyond the nasal valve, whereas the conventional nasal spray administration system provides for initial deposition of only about 41% of the dose as initially deposited in the nasal cavity in these segments. In particular, following administration, the conventional nasal spray administration system provides for initial deposition of only about 13% of the dose as initially deposited in the nasal cavity in the upper posterior region of the nasal cavity, whereas the bi-directional liquid jet administration system provides for initial deposition of about 52% (SD 9%) of the dose as initially deposited in the nasal cavity to the upper posterior region of the nasal cavity and the bi-directional powder administration system provides for initial deposition of about 56% (SD 14%) of the dose as initially deposited in the nasal cavity to the upper posterior region of the nasal cavity.

[0226] The results of this study thus support the postulation of the present inventors that the increased concentration of the delivered substance to the CNS for any given blood plasma concentration could at least in part be a function of the relative fractions of substance which are delivered to the anterior and posterior regions of the nasal cavity, and in particular the upper posterior region.

[0227] Finally, it will be understood that the present invention has been described in its preferred embodiments and can be modified in many different ways without departing from the scope of the invention as defined by the appended claims.

[0228] The following references are herein incorporated in their entirety by reference.

[0229] 1. Born, J et al, Sniffing neuropeptides: a transnasal approach to the human brain, Nature Neuroscience, 2002, pages 514 to 516.

[0230] 2. Cole, P, The Respiratory Role of the Upper Airway, Mosby, 1992, pages 7 and 8.

[0231] 3. Einer-Jensen, N et al, Local transfer of diazepam, but not of cocaine, from the nasal cavities to the brain arterial blood in rats, Pharmacol and Toxicol, 2000, Vol 87, pages 276 to 278.

[0232] 4. Einer-Jensen, N et al, Transfer of titrated water, tyrosine and propanol from the nasal cavity to cranial arterial blood in rats, Experimental Brain Research, 2000, vol 130, pages 216 to 220.

[0233] 5. Martens, J et al, Simultaneous determination of midazolam and its metabolites 1-hydroxymidazolam and 4-hydroxymidazolam in human serum using gas chromatography-mass spectrometry, Journal of Chromatography B, 1997, Vol 692, pages 95 to 100.

[0234] 6. Rosenberger, H, Growth and Development of the Naso-Respiratory Area in Childhood, PhD Thesis, Laboratory of Anatomy, School of Medicine, Western Reserve University, Presented to the Annual Meeting of the American Laryngological, Rhinological and Otological Society, Charleston, S.C., USA, 1934.

[0235] 7. Zacharek, M A et al, Sagittal and Coronal Dimensions of the Ethmoid Roof: A Radioanatomic Study, Am J Rhinol 2005, Vol 19, pages 348 to 352.

1-14. (canceled)

15. A method of treating migraine in a subject, comprising:

fitting a mouthpiece to a mouth of the subject;

fitting a nosepiece unit to a first nostril of the subject, wherein the nosepiece unit comprises a nozzle, a delivery channel fluidly connected to the mouthpiece, and a substance supply unit containing a powdered sumatriptan substance;

causing exhalation breath of the subject through the mouthpiece to cause closure of the oropharyngeal velum of the subject and produce a bi-directional flow into one nasal passageway of the subject and out of the other nasal passageway of the subject;

delivering a dose of the powdered sumatriptan substance from the substance supply unit to the nasal airway of the subject through the nozzle when the exhalation flow reaches the predetermined flow rate;

depositing at least 30% of a dose of the powdered sumatriptan substance, as initially deposited in the nasal airway of the subject, to an upper posterior region of the nasal airway of the subject, which is posterior of a nasal valve of the subject and above an inferior meatus of the subject; and

providing a higher local concentration in a cerebrovasculature of the subject and a central nervous system (CNS) effect which is greater than that predicted from a counterpart blood plasma concentration of sumatriptan achieved using intravenous (IV) delivery.

16. The method of claim **15**, wherein at least 40% of the dose as initially deposited in the nasal airway is deposited in the upper posterior region of the nasal airway.

17. The method of claim **15**, wherein at least 50% of the dose as initially deposited in the nasal airway is deposited in the upper posterior region of the nasal airway.

18. The method of claim **15**, wherein the ratio of the peak CNS effect to the peak blood plasma concentration is at least 2 times that achieved using intravenous (IV) delivery.

19. The method of claim **15**, wherein the ratio of the peak CNS effect to the peak blood plasma concentration is at least 3 times that achieved using intravenous (IV) delivery.

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