USE OF MELATONIN ANALOGUES FOR INDUCTION OF GENERAL ANESTHESIA

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References Cited
U.S. PATENT DOCUMENTS

FOREIGN PATENT DOCUMENTS
EP 0 513 702 A2 11/1992

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ABSTRACT
Melatonin (N-acetyl-5-methoxytryptamine), or its biologically active analogues, are used to induce anesthesia.

29 Claims, No Drawings
USE OF MELATONIN ANALOGUES FOR INDUCTION OF GENERAL ANESTHESIA

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of Ser. No. 09/927,687 filed Aug. 10, 2001, now U.S. Pat. No. 6,552,064 which itself is a continuation-in-part of Serial No. 60/233,785 filed Sep. 19, 2000, and this case claims the benefit of those earlier filing dates.

BACKGROUND OF THE INVENTION

In the medical field there is a continuing need for new compounds having demonstrated use for inducing anesthesia. It is not only important to induce beneficial anesthesia, but it must be done in a manner that limits toxicity to patients, and as well, minimizes what is known as “anesthesia hangover”.

The pineal hormone melatonin (N-acetyl-5-c) has several putative functions, including regulation of circadian rhythms, regulation of the reproductive axis and antioxidant activity. Autoradiographic studies and receptor assays have demonstrated the presence of melatonin receptors in various regions of the central nervous system and in other tissues in humans.

Exogenous administration of melatonin has been found by several investigators to facilitate sleep onset and improve quality of sleep. Available data suggest that the sleep-inducing properties of melatonin may differ from those of benzodiazepines. Benzodiazepines decrease duration of REM sleep after single administration of a high dose or long-term administration of low dose. Benzodiazepines also reduce slow-wave sleep, thus negatively influencing sleep quality. In contrast, a single low dose of melatonin produced no suppression of REM sleep. Furthermore, unlike benzodiazepines, melatonin does not induce “hangover” effects.

In a previous publication of one of the inventors, British Journal of Anesthesia 82(6):875–80(1999), low-level dosing of oral melatonin in a sublingual fashion was demonstrated as an effective pre-medication, prior to administering a general anesthetic. Patients who were administered such low-level doses sublingually had a significant decrease in anxiety levels and an increase in levels of sedation before operation. However, as pointed out in that article, the use of melatonin in anesthesia had as of then never been evaluated properly, and to the inventor’s present knowledge it has never been used as a general anesthetic prior to this series of applications.

The invention of Ser. No. 09/927,687 had as its primary objective the development of pineal hormone melatonin (N-acetyl-5-methoxytryptamine) or its biologically active analogues as a general anesthetic which can be used without any significant anesthetic hangover. The continuing need in the art for meeting that objective was readily apparent.

With reference to the continuing need referred to above, applicants have continued to work with melatonin and its analogues to derive improved compounds which may be used for anesthetic effect generally and in small doses for hypnotic effect sedation or even sleep induction. This continuing work has evolved into the discovery that 2-trihalo methyl melatonins and in particular the 2-trifluoromethylmelatonin are substantially more active in anesthetic effect than melatonin itself. The result of this increased activity means that the compounds may be used in larger doses for general anesthesia, but in smaller doses for hypnotic effect and sedation and sleep effect.

Further discoveries since the filing of the original application have revealed a particularly effective pharmaceutical carrier for melatonin, melatonin analogues and the improved derivatives of the present invention. The carrier allows dissolving and high concentrations of melatonin or its analogues. The preferred carrier is comprised of one volume of 1-methyl-2-pyrrolidinone, one volume of propylene glycol and two volumes of water. It goes without saying that the volumetric ratios of these carrier solvents may be varied somewhat, depending upon the circumstances.

SUMMARY OF THE INVENTION

Anesthetic compositions are prepared using a pharmaceutically-acceptable carrier, preferably a preferred carrier comprising a mixture of one volume of 1-methyl-2-pyrrolidinone, one volume of propylene glycol and two volumes of water and an anesthetic-inducing effective amount of melatonin or biologically active analogues of melatonin such as 2-trifluoromethylmelatonin. The invention also relates to the method of administration using the described compositions.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

N-acetyl-5-methoxytryptamine (melatonin) is synthesized mainly by the pineal gland, and to a lesser extent by extra pineal tissues such as the retina, hardier gland, and gastrointestinal tract. Melatonin has the following structure:

\[
\text{CH}_3\text{O} \quad \text{CH}_2\text{CH}_2\text{N} \quad \text{NCOCH}_3
\]

As seen, the chemical formula for melatonin is N-acetyl-5-methoxytryptamine. From time to time in the specification applicant uses the term “N-acetyl-5-methoxytryptamine (melatonin), or its biologically active analogues”. As used herein, this phrase refers to the precise compound itself and other compounds having the same general structure, but only differing in minor moieties, and therefore still having the same biological activity of anesthetic-inducing effectiveness. The biologically active compound of the present invention, such as melatonin, may be derived or extracted from the pineal gland, or it can be synthetized from 5-Methoxyindol as a starting material by known routes, Szmuszkovicz et al., J. Org. Chem. 25, 857 (1960). Biological role of melatonin: Chem. & Eng. News 45, 40 (May 1, 1967).

The analogue of the present invention that has been found to be more active than melatonin itself, and therefore can be used in smaller dosage levels and even at such small dosage levels to effectively induce hypnotic state, sedation or sleep, is 2-trifluoromethylmelatonin. As can be seen from a comparison with the formula for melatonin it contains a carbon trifluoromethyl moiety at the 2-position, replacing a hydrogen moiety from melatonin. While 2-trifluoromethylmelatonin is the most effective so far found to date, it may be that other 2-position moieties such as 2-trihalo moieties in general can be used. Therefore, within the term 2-trihalo we intend to encompass chloride, fluoride, bromide and iodide.
The anesthetic active, i.e., the N-acetyl-5-methoxytryptamine (melatonin), or its biologically active analogues, can be administered with traditionally acceptable pharmaceutical carriers as described in the patent applications. Examples include Intralipid®, Cyclodextrin, and others, some of which are briefly hereinafter described. However, there is no need for detailed description of suitable anesthetic carriers because they are so well known in the industry. Here, however, the present applicants have discovered a preferred pharmaceutical carrier system.

Melatonin has previously been administered to animals in organic solvents that have central nervous system (CNS) effects. Such organic solvents frequently consist of ethanol in water. An administration vehicle not having CNS effects is desired for the administration of melatonin to achieve pure melatonin effects.

It was discovered that melatonin could be dissolved in high concentrations in a solvent comprised of 1 volume 1-methyl-2-pyrrolidinone, 1 volume propylene glycol and 2 volumes of water. Melatonin can be dissolved up to a concentration of 300 mg/ml in this solvent. The volume ratios here expressed are preferred but generally can be within the range of 25% or less by volume of 1-methyl-2-pyrrolidinone.

Intravenous administration of melatonin in this solvent system results in a rapid increase in blood melatonin concentrations in rats that are suitable to cause an unexpected anesthetic effect without causing toxic side effects.

Formulations containing melatonin analogues that consist of melatonin or its analogues and 1-methyl-2-pyrrolidinone in water can be used or formulations containing melatonin analogues and 1-methyl-2-pyrrolidinone combined with water and other known inert solvents such as propylene glycol, propyglypypglycol, polysorbants and cyclodextrins can be used.

Derivatives or analogues of melatonin, such as 2-bromomelatonin and 2-phenylmelatonin may be administered in solvents described above containing 1-methyl-2-pyrrolidinone for delivery to mammals.

As earlier expressed, 1-methyl-2-pyrrolidinone may be present in the disclosed vehicles at concentrations less than 25% volume/volume. For example, concentrations of 1-methyl-pyrrolidinone may range from 5 to 25% or greater than 25% in water, or in water combined with propylene glycol, glycerol, dextrins and/or polysorbants.

The composition may be administered by conventional administration methods for anesthetics, i.e., oral administration, nasal respiratory administration, bolus injection, intravenous administration by repeated doses or by continuous infusion, rectal, vaginal, sublingual, cutaneous and slow release routes. It may be, and often is preferred, that it be administered in two or more ways, such as by bolus injection followed by continuous intravenous administration.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a melatonin biologically active analogue as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylene sorbitan (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infortrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition, or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the toxicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0 µm, particularly 0.1 and 0.5 µm, and have a pH in the range of 5.5 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing an active compound with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in
preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device, or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The anaesthetic may be used alone or often in combination with other anaesthetics simultaneously administered. But another way, it will be appreciated that when using any combination described herein, both the compound of melatonin or its analogue and the other active agent(s) can be administered to a patient, within a reasonable period of time. It may indeed act synergistically with other anaesthetic drugs. The compounds may be in the same pharmaceutically acceptable carrier and therefore administered simultaneously. They may be in separate pharmaceutical carriers such as conventional oral dosage forms which are taken simultaneously. The term “combination” also refers to the case where the compounds are provided in separate dosage forms and are administered sequentially. Therefore, by way of example, one active compound may be administered as a tablet and then, within a reasonable period of time, the second active component may be administered either as an oral dosage form such as a tablet or a fast-dissolving oral dosage form. By a “fast dissolving oral formulation” is meant, an oral delivery form which, when placed on the tongue of a patient, dissolves within about 10 seconds.

The dosage will vary depending upon the deepness of the anaesthesia desired, but based upon limited studies to date, it is believed that the dosage most effective will be within the range of 0.001 mg/kg of body weight to about 500 mg/kg of body weight, more predictably preferred is the range of 5 mg/kg of body weight to about 350 mg/kg of body weight.

The synthesis of 2-trifluoromethylmelatonin may be summarized by the following reaction scheme.

![Chemical structure diagram]

In word description, the reaction synthesis of 2-trifluoromethylmelatonin can be described as follows. 2-Iodomelatonin (1 g, FW=232) was dissolved in 20 ml DMF in a round bottom glass reaction flask fitted with a condenser. Cul (1.3 g, FW=190) and methyl 2,2-difluoro-2-(fluorosulfonyl)benzoate (1.2 g, FW=192) was added and the reaction mixture heated to 60–80°C at least 3 hr.

Following the reaction period, the reaction mixture was chilled on ice and DMF removed from the mixture by rotatory evaporation. 15 ml water was added and the reaction mixture neutralized. Melatonin products were extracted from the aqueous phase with methylene chloride (20 ml×2). The products of the reaction were analyzed by GC/MS and found to contain a fraction that corresponds to trifluoromethylmelatonin (M*, m/z 300).

Trifluoromethylmelatonin analysis was performed by silica gel TLC (Silica Gel 60, Fisher Scientific, Inc.) using anhydrous ethyl acetate as mobile phase. Bands were detected by fluorescence (366 nm). Isolation of one band yielded pure trifluoromethylmelatonin. Recovery and weighing of the fraction demonstrates a yield of greater than 25–30%. 2-Trifluoromethylmelatonin was confirmed by proton and fluorine NMR. When patients are administered N-acetyl-5-methoxytryptamine (melatonin) or its biologically active analogues, there is a noticeable decrease in anaesthetic hangover. It is believed that this occurs because melatonin itself is a naturally-occurring hormone synthesized in the body by the pineal gland.

The following anaesthetic examples are offered to further illustrate, but not limit the invention disclosed herein.

**EXAMPLES**

All experiments were carried out in male Sprague-Dawley rats (300–350 g). Rats were maintained on a 12 hour light/12 hour dark cycle with free access to food and water. All surgical procedures were performed under sterile conditions (skin preparation, sterile filled drape, gloves, mask, etc.). All instruments and materials were ethylene oxide sterilized. Non-fastening adult male Sprague Dawley rats (~300 gm) were anesthetized with halothane in oxygen and weighed. The hair over the ventral neck and over the back (between the scapulae) was removed with an electric razor. In the supine position the ventral neck was washed with povidone-iodine, followed by a 3-cm skin incision, just left of midline. All bleeding points were cauterized. Both the left jugular vein and left common carotid artery were isolated via blunt dissection. The left jugular vein was cannulated with a heparinized (20 U/ml) saline-filled silastic catheter (0.012-in ID, 0.025-in OD) advanced ~3 cm into the right atrium. The jugular catheter was secured to the vein with 4-0 silk at the point of insertion, as well as at the rostral jugular ligature.

After implantation of intravascular catheters, rats were housed in individual stainless steel cages. Studies with melatonin were carried out 5–7 days after surgery. Crystaline Melatonin powder was obtained from Sigma (Sigma Chemical Co. St. Louis, Mo.).

The melatonin was prepared for anaesthetic use in the following manner:

100 mg melatonin added to 1 ml of intralipid and 1 ml of Ringer's Lactate (final concentration=50 mg melatonin/ml).

**Results**

**Rat 1:** 250 mg/kg followed approximately 1 minute later by 65 mg/kg: the animal was very drugged but did not lose righting reflex.

**Rat 2:** 250 mg/kg resulted in loss of righting and eyelash reflexes and inability to pull his hind paw in response to pressure applied to it.

**Rat 3:** 320 mg/kg resulted in loss of righting and eyelash reflexes and inability to pull his hind paw in response to pressure applied to it.

**Rat 4:** 370 mg/kg resulted in loss of righting and eyelash reflexes and inability to pull his hind paw in response to pressure applied to it.
Additional preparation of melatonin occurred with cyclo-
dextrin as follows:
100 mg melatonin added to 1 ml of cycloextrin 40% and 1
ml of Intralipid (final concentration=50 mg melatonin/ml)
Results
1 Rat 1: 315 mg/kg: the animal moves slowly but no loss of
righting reflex.
2 Rat 2: 460 mg/kg resulted in loss of righting reflex.
Another group of rats received the solvent alone and did not
result in any effect. This demonstrates the anesthetic prop-
erty of melatonin, and that the invention accomplishes its
stated objectives.
Melatonin in 40% Cycloextrin
1 Rat 1: 315 mg/kg resulted in ptosis, loss of eye blink
response and loss of paw pinch response to a pressure of
60 mmHg using a very low profile load cell (Omega part
number LCKD-1KG, measurement range of 0–1 kg) from
OMEGA Engineering, INC. One Omega Drive, Stamford,
Conn. 06907-0047. The righting reflex was lost for 27
min.
2 Rat 2: 374 mg/kg resulted in ptosis and loss of eye blink
response. The righting reflex was lost for 15 min. The
animal responded to a paw pinch response to a pressure of
60 mmHg by pulling his paw without vocalization.
3 Rat 3: Administration of the solvent (40% cycloextrin) did
not affect the animal behavior and did not result in
sedation or hypnosis.
In a recent publication of the inventor concerning this
invention, additional data relating to the invention is
disclosed, Anesthesia and Analgesia, 91:473–479(2000), the
disclosure of which is incorporated herein by reference.
The following examples are comparative examples dem-
strating the effectiveness of melatonin for induction of
general anesthesia in rats and how it compares to other
known anesthetics in inducing general anesthesia.
COMPARATIVE EXAMPLES
The goal of these examples was to determine the doses of
melatonin, thiopental and propofol needed to induce anes-
thesia in 50% and 95% of rats and to evaluate the time
course of different indices of anesthesia. Rats were randomly
assigned to receive three cumulative doses of 6.67 mg/kg i.v.
thiopental, 3.3 mg/kg i.v. propofol or 70 mg/kg i.v. melato-
nin or three cumulative injections of the vehicle in which
these drugs were dissolved at intervals of approximately 1
min. After the final cumulative dose, measurements of
anesthesia end-points were made at fixed intervals for an
additional 20 minutes. Separate groups of rats received a
single bolus injection of 20 mg/kg i.v. thiopental, 10 mg/kg
i.v. propofol or 275 mg/kg i.v. of melatonin or the vehicle in
which these drugs were dissolved. Measurements of anes-
thetia end-points were made in these rats at fixed intervals
for 20 minutes. Righting reflex was scored on a four-point
scale (1=immediate/brisk, both feet under the rat; 2=complete, but slower than normal; 3=slow, feet not placed
under body; and 4=absent). The threshold pressure (mm Hg)
at which the rat withdrew or vocalized after pinch of one
hindpaw was measured. For paw pinch, a subminiature, very
low profile load cell Omega part number LCKD-1KG,
measurement range of 0–1 kg) (OMEGA Engineering, INC.,
Stamford, Conn.) was used to measure the amount of
pressure applied to the rat’s paw. The action of compressing
the load cell between the faces of the sponge clamp assem-
bly results in a change in impedance within the load cell, and
this in turn, was then converted to mm Hg pressure by the
monitor. The presence or absence of eyelash reflex was
noted on a three-point scale (1=normal, 2=weak; and
3=absent). The strength of grip by the forepaws was deter-
mined on a four-point scale (0=absent, 1=weak, 2=moderate
and 3=strong).
Thiopental was purchased from Abbott Laboratories
(Northern Chicago, Ill.). Propofol was purchased from Zen-
eca Pharmaceuticals (Wilmington, Del.). Melatonin was
purchased from Sigma Chemical Co. (St. Louis, Mo.).
Thiopental and propofol were dissolved in saline and Intralipid™ respectively. Melatonin was dissolved in a mix-
ture comprising 25% v/v propylene glycol and 25% v/v
1-methyl-2-pyrrolidinone in sterile water. For the cumula-
tive injections, the individual doses were administered in
a volume of 0.2 ml and the maximum volume of drug injected
did not exceed 0.6 ml. For the bolus injections, the volume
of drug injected ranged from 0.6 to 0.75 ml.
Intravenous injection of saline, Intralipid™ or the vehicle
for melatonin did not affect righting reflex, grip strength, or
eyelash reflex. Neither saline nor Intralipid™ altered paw
withdrawal threshold. However, the vehicle for melatonin
produced a significant short-lived increase in paw with-
drawal threshold that subsequently decreased to near base-
line levels.
Cumulative i.v. injection of divided doses of thiopental
caused a progressive loss of righting reflex, grip strength
and eyelash reflex with an estimated ED₅₀ (and 95% CI) for
the loss of righting reflex of 23.8 (15.4–36.7) mg/kg i.v. Bolus
injection of 20 mg/kg thiopental resulted in an immediate
loss of righting reflex and grip strength that was maximal at
1 min and resolved within 15 min. These effects were not
accompanied by a change in paw withdrawal threshold.
Cumulative i.v. injection of divided doses of propofol
caused a progressive loss of righting reflex, grip strength
and eyelash reflex with an estimated ED₅₀ (and 95% CI) for
loss of righting reflex of 14.9 (6.4–34.9) mg/kg. Bolus injection
of 10 mg/kg i.v. propofol caused an immediate loss of
righting reflex and grip strength that was maximal for 5 min
and resolved within 10 min. These effects were accom-
plished by a significant increase in paw withdrawal thresh-
old of similar duration.
Cumulative i.v. injection of divided doses of melatonin
caused a progressive loss of righting reflex and grip strength,
but did not appreciably blunt the eyelash reflex. It also
dose-dependently increased paw withdrawal threshold. The
estimated ED₅₀ (and 95% CI) of melatonin for loss of
righting reflex was 312 (205–476) mg/kg i.v. Bolus injection
of 275 mg/kg i.v. melatonin resulted in an immediate loss of
righting reflex and grip strength that was maximal for 5 min
and resolved to near baseline values by 15 min. This dose of
melatonin also increased paw withdrawal threshold as com-
pared to vehicle. The increase in paw withdrawal threshold
persisted for at least 20 min, and was apparent at doses of
140 mg/kg or greater.
This data demonstrates that intravenous administration
of melatonin or its analogues can induce general anesthesia.
This anesthesia is accompanied by an analgesia that persists
after the return of consciousness.
What is claimed is:
1. An anesthetic composition comprising:
a pharmaceutically acceptable anesthetic carrier, and an
anesthetic inducing effective amount of a
2-trihalomethylmelatonin.
2. The composition of claim 1 wherein the halo moiety in
2-trihalomethylmelatonin is selected from the group con-
sisting of chloride, fluoride, bromide, iodide and combina-
tions thereof.
3. The composition of claim 2 wherein the
2-trihalomethylmelatonin is 2-trifluoromethylmelatonin.
4. The anesthetic composition of claim 1 wherein the amount of 2-trihalomethylmelatonin is sufficient to provide a dose of from about 0.001 mg/kg of body weight to about 500 mg/kg of body weight.

5. The anesthetic composition of claim 1 wherein the amount of 2-trihalomethylmelatonin is sufficient to provide a dose of from about 5 mg/kg of body weight to about 350 mg/kg of body weight.

6. A method of inducing sedative effect as well as general anesthesia, comprising:
   administering to a mammal an effective amount of 2-trihalomethylmelatonin.

7. The method of claim 6 wherein the active anesthetic is 2-trifluoromethylmelatonin.

8. The method of claim 6 wherein the amount of 2-trihalomethylmelatonin administered is a dose of from about 0.001 mg/kg of body weight to about 500 mg/kg of body weight.

9. The method of claim 6 wherein the amount of 2-trihalomethylmelatonin administered is from about 5 mg/kg of body weight to about 350 mg/kg of body weight.

10. The method of claim 6 wherein the administering is by a method selected from the group consisting of oral administration, nasal respiratory administration, bolus injection, intravenous administration, continuing infusion, rectal, vaginal, sublingual and cutaneous administration.

11. The method of claim 10 wherein the administration is by an initial bolus injection, followed by intravenous administration.

12. The method of claim 6 wherein the administration is in combination with simultaneous administration of another anesthetic.

13. The method of claim 6 wherein the 2-trihalomethylmelatonin is derived from melatonin which is secreted from the pineal gland.

14. An anesthetic composition comprising:
   a pharmaceutically acceptable carrier which is a mixed solvent of 1-methyl-2-pyrrolidinone, propylene glycol and water, and an anesthetic inducing effective amount of 2-trihalomethylmelatonin.

15. An anesthetic composition of claim 14 wherein the carrier is 1 volume part of 1-methyl-2-pyrrolidinone, 1 volume part of propylene glycol and 2 volume parts of water.

16. The anesthetic composition of claim 14, wherein the anesthetic carrier is water mixed with an anesthetic carrier selected from the group consisting of 1-methyl-2-pyrrolidinone, propylene glycol, polypropylene glycol, polysorbates and cyclodextrins.

17. An anesthetic composition comprising:
   a pharmaceutically acceptable anesthetic carrier, and an anesthetic inducing effective amount of 2-phenylmelatonin.

18. The anesthetic composition of claim 17 wherein the amount of compound is sufficient to provide a dose of from about 0.001 mg/kg of body weight to about 500 mg/kg of body weight.

19. The anesthetic composition of claim 17 wherein the amount of compound is sufficient to provide a dose from about 5 mg/kg of body weight to about 350 mg/kg of body weight.

20. A method of inducing general anesthesia, comprising:
   administering to a mammal an effective amount of a compound selected from the group consisting of 2-bromomelatonin and 2-phenylmelatonin.

21. The method of claim 20 wherein the amount of a compound administered is a dose of from about 0.001 mg/kg of body weight to about 500 mg/kg of body weight.

22. The method of claim 20 wherein the amount of a compound administered is a dose from about 5 mg/kg of body weight to about 350 mg/kg of body weight.

23. An anesthetic composition comprising:
   a pharmaceutically acceptable carrier which is a mixed solvent of 1-methyl-2-pyrrolidinone, propylene glycol and water and an anesthetic inducing effective amount of 2-phenylmelatonin.

24. The anesthetic composition of claim 23 wherein the carrier is 1 volume part of 1-methyl-2-pyrrolidinone, 1 volume part of propylene glycol and 2 volume parts of water.

25. The anesthetic composition of claim 24 wherein the anesthetic carrier is water mixed with an anesthetic carrier selected from the group consisting of 1-methyl-2-pyrrolidinone, propylene glycol, polypropylene glycol, polysorbates and cyclodextrins.

26. The method of claim 20 wherein the compound is derived from melatonin which is secreted from the pineal gland.

27. The method of claim 20 wherein the administering is by a method selected from the group consisting of oral administration, nasal respiratory administration, bolus injection, intravenous administration, continuing infusion, rectal, vaginal, sublingual and cutaneous administration.

28. The method of claim 27 wherein the administration is by an initial bolus injection, followed by intravenous administration.

29. The method of claim 20 wherein the administration is in combination with simultaneous administration of another anesthetic.

* * * * *