METHODS OF TREATMENT USING A DEXMEDETOMIDINE PREMIX FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of and claims priority under 35 U.S.C. §120 to U.S. Serial No. 13/541,524 filed July 3, 2012, which is a continuation of U.S. Serial No. 13/343,672 filed January 4, 2012, now U.S. Patent No. 8,242,158, the contents of each of which are hereby incorporated by reference in their entireties, and to each of which priority is claimed.

1. FIELD OF THE INVENTION

[0001] The present invention relates to patient-ready, premixed formulations of dexmedetomidine, or a pharmaceutically acceptable salt thereof, that can be used, for example, in perioperative care of a patient or for sedation.

2. BACKGROUND OF THE INVENTION

[0002] Racemic 4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole, which is known under the name medetomidine, is a selective and potent α_2-adrenoceptor agonist. Medetomidine has been used as an antihypertensive agent and as a sedative-analgesic agent. It has further been observed that this compound also possesses anxiolytic effects and can therefore be used in the treatment of general anxiety, panic disorder and various types of withdrawal symptoms.

[0003] The d-enantiomer of medetomidine, the generic name of which is dexmedetomidine, is described in U.S. Pat. No. 4,910,214 as an α_2-adrenoceptor agonist for general sedation/analgesia and the treatment of hypertension or anxiety. U.S. Pat. Nos. 5,344,840 and 5,091,402 discuss dexmedetomidine in perioperative and epidural use, respectively. For example, when used in perioperative care, dexmedetomidine can reduce the amount of anesthetic necessary to anesthetize a patient. Additionally, U.S. Pat. No. 5,304,569 discusses the use of dexmedetomidine in treating glaucoma, and U.S. Pat. No. 5,712,301 discusses the use of dexmedetomidine for preventing neurodegeneration caused by ethanol consumption. Furthermore, U.S. Pat. No. 6,716,867 discloses methods of sedating a patient while in an intensive care unit by administering dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the patient.

[0004] Dexmedetomidine can be administered to a patient in a variety of ways. For example, U.S. Pat. Nos. 4,544,664 and 4,910,214 disclose the administration of dexmedetomidine via parenteral, intravenous, and oral routes. U.S. Pat. No. 4,670,455 describes intramuscular and intravenous administration, while U.S. Pat. Nos. 5,124,157 and 5,217,718 describe a method and device for administering dexmedetomidine through the skin. Additionally, U.S. Pat. No. 5,712,301 states that dexmedetomidine can be administered transmucosally.

[0005] To date, dexmedetomidine has been provided as a concentrate that must be diluted prior to administration to a patient. The requirement of a dilution step in the preparation of the dexmedetomidine formulation is associated with additional costs and inconvenience, as well as the risk of possible contamination or overdose due to human error. Thus, a dexmedetomidine formulation that avoids the expense, inconvenience, delay and risk of contamination or overdose would provide significant advantages over currently available concentrated formulations.

3. SUMMARY OF THE INVENTION

[0006] The present invention relates to premixed pharmaceutical compositions of dexmedetomidine, or a pharmaceutically acceptable salt thereof, that are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration. Thus, the compositions of the present invention are formulated as a premixed composition comprising dexmedetomidine.

[0007] In certain non-limiting embodiments, the premixed dexmedetomidine composition is a liquid comprising dexmedetomidine, or a pharmaceutically acceptable salt thereof, at a concentration of between about 0.05 μg/mL and about 15 μg/mL.

[0008] In other non-limiting embodiments, the premixed dexmedetomidine composition is a liquid comprising dexmedetomidine at a concentration of about 4 μg/mL.

[0009] In other non-limiting embodiments, the premixed dexmedetomidine composition comprises dexmedetomidine mixed or dissolved in a sodium chloride saline solution.

[0010] In certain embodiments, the premixed dexmedetomidine composition is disposed within a sealed container or vessel.

[0011] In certain embodiments, the dexmedetomidine composition is disposed in a container or vessel and is formulated as a premixture.

[0012] In certain embodiments, the premixed dexmedetomidine composition is disposed within a sealed container as a total volume of about 20 mL, 50 mL or 100 mL.

[0013] In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention comprises dexmedetomidine, or a pharmaceutically acceptable salt thereof, at a concentration of between about 0.05 μg/mL and about 15 μg/mL, and sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.

[0014] In other non-limiting embodiments, the premixed dexmedetomidine composition of the present invention comprises dexmedetomidine, or a pharmaceutically acceptable salt thereof, at a concentration of about 4 μg/mL and sodium chloride at a concentration of about 0.90 weight percent.

[0015] In certain embodiments, the compositions of the present invention are formulated as a pharmaceutical composition for administration to a subject for sedation, analgesia or treatment of anxiety or hypertension.

[0016] The present invention also relates to the perioperative treatment of a patient to reduce the response of the autonomic nervous system to stimuli during an operation by administering a dexmedetomidine composition of the invention.

[0017] In other non-limiting embodiments, the dexmedetomidine compositions of the present invention can be administered as an anxiolytic analgesic to a patient. In certain embodiments, the composition can be administered as a premedication prior to an operation with or without administration of an amount of an anesthetic effective to achieve a desired level of local or general anesthesia.

[0018] In other non-limiting embodiments, the dexmedetomidine compositions of the present invention can be administered as a sedative. In certain embodiments, the composition is administered preoperatively to potentiate the effect of an anesthetic, wherein administration of the composition reduces the amount of anesthetic required to achieve a desired level of anesthesia.

[0019] In certain embodiments of the present invention, the premixed dexmedetomidine composition is administered parenterally as a liquid, orally, transdermally, intravenously, intramuscularly, subcutaneously, or via an implantable pump.

4. DETAILED DESCRIPTION

[0020] The present invention is based in part on the discovery that dexmedetomidine prepared in a premixed formulation that does not require reconstitution or dilution prior to administration to a patient, remains stable and active after prolonged storage. Such premixed formulations therefore avoid the cost, inconvenience, and risk of contamination or overdose that can be associated with reconstituting or diluting a concentrated dexmedetomidine formulation prior to administration to a patient.

[0021] For clarity and not by way of limitation, this detailed description is divided into the following sub-portions:

(4.1) Definitions;

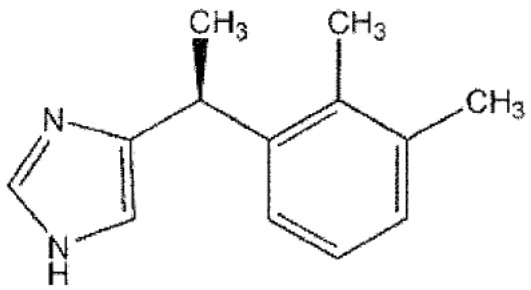
(4.2) Pharmaceutical formulations; and

(4.3) Methods of using premixed dexmedetomidine compositions.

4.1 Definitions

[0022] The terms used in this specification generally have their ordinary meanings in the art, within the context of this invention and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner in describing the compositions and methods of the invention and how to make and use them.

[0023] According to the present invention, the term "dexmedetomidine" as used herein refers to a substantially pure, optically active dextrorotary stereoisomer of medetomidine, as the free base or pharmaceutically acceptable salt. In one, non-limiting embodiment, dexmedetomidine has the formula (S)-4-[1-(2,3-dimethylphenyl)ethyl]-3H-imidazole. A pharmaceutically acceptable salt of dexmedetomidine can include inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid. Preferably, the dexmedetomidine salt is dexmedetomidine HCl. In other non-limiting embodiments, dexmedetomidine comprises the structure depicted below in Formula I:



Formula I

[0024] The terms "premix" or "premixture" as used herein refers to a pharmaceutical formulation that does not require reconstitution or dilution prior to administration to a patient. For example, in contrast to non-premixed formulations of dexmedetomidine, the premixed compositions provided herein are suitable for administration to a patient without dilution by, for example, a clinician, hospital personnel, caretaker, patient or any other individual.

[0025] In certain embodiments, the compositions of the present invention can be formulated as "ready to use" compositions which refer to premixed compositions that are suitable for administration to a patient without dilution. For example, in certain embodiments, the compositions of the present invention are "ready to use" upon removing the compositions from a sealed container or vessel.

[0026] In certain embodiments, the compositions of the present invention can be formulated as a "single use dosage," which refers to a premixed composition that is disposed within a sealed container or vessel as a one dose per container or vessel formulation.

[0027] According to the invention, a "subject" or "patient" is a human, a non-human mammal or a non-human animal. Although the animal subject is preferably a human, the compounds and compositions of the invention have application in veterinary medicine as well, *e.g.*, for the treatment of domesticated species such as canine, feline, and various other pets; farm animal species such as bovine, equine, ovine, caprine, porcine, etc.; wild animals, *e.g.*, in the wild or in a zoological garden; and avian species, such as chickens, turkeys, quail, songbirds, etc.

[0028] The term "purified" as used herein refers to material that has been isolated under conditions that reduce or eliminate the presence of unrelated materials, i.e., contaminants, including native materials from which the material is obtained. As used herein, the term "substantially free" is used operationally, in the context of analytical testing of the material.

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