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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

HOSPIRA, INC. and ORION CORPORATION,	)	
Plaintiffs,	)	Civil Action No. 3:09-cv-04951 (MLC) (TJB)
v.	)	
SANDOZ INTERNATIONAL GmbH, SANDOZ INC., and SANDOZ CANADA INC.,	)	**REDACTED VERSION**
Defendants.	)	

AMENDED COMPLAINT

Plaintiffs Hospira, Inc. ("Hospira") and Orion Corporation ("Orion") (collectively "Plaintiffs") for their Complaint against Defendants Sandoz International GmbH, Sandoz Inc., and Sandoz Canada Inc. (collectively "Defendants" or "Sandoz") hereby allege as follows:

PARTIES

1. Hospira is a Delaware corporation with its principal place of business at 275 North Field Drive, Lake Forest, Illinois 60045.

2. Orion is a corporation organized under the laws of Finland with its principal place of business at Orionintie 1A, FI-02200 Espoo, Finland.

3. On information and belief, Defendant Sandoz International GmbH is a German corporation with a principal place of business at Industriestrasse 25, Holzkirchen 83607, Germany.

4. On information and belief, Defendant Sandoz Inc. is a corporation organized and existing under the laws of the State of Colorado with places of business at 2555 West Midway Boulevard, Broomfield, Colorado 80020 and at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540.

5. On information and belief, Defendant Sandoz Canada Inc. is a corporation organized and existing under the laws of Canada with a principal place of business at 145 Jules-Léger, Boucherville, Quebec J4B 7K8, Canada.

6. On information and belief, Defendant Sandoz International GmbH conducts its United States business operations, in part, through Defendant Sandoz Inc.

7. On information and belief, Defendant Sandoz Inc. is the United States arm of Defendant Sandoz International GmbH.

8. On information and belief, Defendant Sandoz Inc. is a subsidiary of Defendant Sandoz International GmbH, and the two companies have at least one common officer and/or director.

9. On information and belief, Defendant Sandoz Inc. is controlled and/or dominated by Defendant Sandoz International GmbH.

10. On information and belief, the acts of Defendant Sandoz Inc. complained of herein were done at the direction of, with the authorization of, and with the cooperation, participation and awareness of, and at least in part for the benefit of, Defendant Sandoz International GmbH.

11. On information and belief, Defendant Sandoz Canada Inc. conducts business in the United States, in part, through and/or with Defendant Sandoz Inc.

12. On information and belief, Defendant Sandoz Canada Inc. develops and manufactures generic pharmaceutical products and directly, or indirectly through Sandoz Inc., markets, distributes, and sells its generic pharmaceutical products throughout the United States.

13. On information and belief, Defendant Sandoz Canada Inc. has sought and obtained FDA approval to market, distribute, and sell generic pharmaceutical products throughout the United States, including at least granisetron hydrochloride for injection, haloperidol, metoprolol tartrate, and ondansetron, and marketed them throughout the United States through and/or with Defendant Sandoz Inc.

14. On information and belief, the acts of Defendant Sandoz Inc. complained of herein were done at the direction of, with the authorization of, and with the cooperation, participation and awareness of, and/or at least in part for the benefit of, Defendant Sandoz Canada Inc.

NATURE OF THE ACTION

15. This is a civil action for infringement of U.S. Patent Nos. 4,910,214 (the "'214 patent") and 6,716,867 (the "'867 patent"). The '214 and '867 patents are attached as Exhibits A and B, respectively.

16. This action is based upon the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* and arises out of Defendants' filing of an Abbreviated New Drug Application ("ANDA") seeking approval to sell dexmedetomidine hydrochloride injection 100 mcg base/ml prior to the expiration of patents assigned to and/or exclusively licensed by Plaintiffs and listed

in the publication entitled *Approved Drug Products with Therapeutic Equivalents* (the "Orange Book") as covering PRECEDEX™.

JURISDICTION AND VENUE

17. This action arises under the patent laws of the United States, 35 U.S.C. § 1 *et seq.*

18. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

19. Defendant Sandoz International GmbH is subject to personal jurisdiction in this District by virtue of, *inter alia*, its direction and control of the business of Sandoz Inc. through which it conducts business in this District, purposefully avails itself of the rights and benefits of New Jersey law, and has substantial and continuing contacts with the state of New Jersey.

20. Defendant Sandoz Inc. is subject to personal jurisdiction in this District by virtue of, *inter alia*, its conduct of business in this District, the location of its place of business in this District, its purposeful availment of the rights and benefits of New Jersey law, and its substantial and continuing contacts with the state of New Jersey.

21. Defendant Sandoz Canada Inc. is subject to personal jurisdiction in this District by virtue of, *inter alia*, its conduct of business in this District directly, or indirectly with Sandoz Inc., its continuous and systematic contacts and business relationship with respect to the accused infringing acts with Sandoz Inc., headquartered in New Jersey, Sandoz Canada's purposeful availment of the rights and benefits of New Jersey law, and/or its substantial and continuing contacts with the state of New Jersey.

22. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b), (c) and (d), and 1400(b).

THE PATENTS-IN-SUIT

23. The '214 patent, entitled "Optical Isomer of an Imidazole Derivative Medetomidine as an Alpha-2-Receptor Agonist," was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on March 20, 1990. Orion is the current assignee of the '214 patent and owns the entire right, title, and interest in the '214 patent.

24. Hospira is the exclusive licensee in the United States of the '214 patent.

25. The '867 patent, entitled "Use of Dexmedetomidine for ICU Sedation," was duly and legally issued by the USPTO on April 6, 2004. Hospira and Orion are co-assignees of the '867 patent and share ownership of the '867 patent.

26. Hospira is the exclusive licensee in the United States of Orion's ownership interest in the '867 patent.

27. Hospira is the holder of New Drug Application ("NDA") No. 21-038, for dexmedetomidine hydrochloride injection 100 mcg base/ml, sold in the United States under the trademark PRECEDEX™. The United States Food and Drug Administration ("FDA") approved NDA No. 21-038 on December 17, 1999.

28. The '214 and '867 patents (collectively "the patents-in-suit") are duly listed in the Orange Book as covering PRECEDEX™. The claims of the '214 and '867 patents cover, *inter alia*, PRECEDEX™, including formulations of PRECEDEX™ and various methods of using PRECEDEX™.

ACTS GIVING RISE TO THIS ACTION

29. On information and belief, Defendants reviewed the patents-in-suit and certain commercial and economic information regarding Hospira's PRECEDEX™ and decided to file an ANDA seeking approval to market a generic version of PRECEDEX™.

30. On information and belief, Defendants collaborated in the research, development, preparation, and filing of ANDA No. 91-465 for generic dexmedetomidine hydrochloride injection 100 mcg base/ml.

31. [redacted]

32. [redacted]

33. [redacted]

34. On information and belief, Defendant Sandoz Inc. manufactures only oral-dosage generic pharmaceutical products.

35. On information and belief, Defendant Sandoz Canada Inc. manufactures injectable generic pharmaceutical products.

36. On information and belief, Defendant Sandoz Canada Inc. has received FDA approval to market, distribute, and sell injectable generic pharmaceutical products.

37. On information and belief, Defendant Sandoz Inc., Princeton NJ 08540, marketed, distributed, and/or sold injectable generic pharmaceutical products for which Defendant Sandoz Canada Inc. received FDA approval.

38. On information and belief, Defendant Sandoz Canada Inc. will be the manufacturer of the injectable, generic version of PRECEDEX™.

39. On information and belief, Defendant Sandoz Inc., Princeton NJ 08540 will market, distribute, and/or sell the injectable, generic version of PRECEDEX™.

40. Plaintiffs received a letter dated July 27, 2009 from Defendant Sandoz Inc. notifying them that Defendant Sandoz Inc. had filed ANDA No. 91-465 with the FDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA") seeking approval to market a generic version of Hospira's PRECEDEX™ prior to the expiry of the patents-in-suit.

41. The stated purpose of Defendant Sandoz Inc.'s July 27, 2009 letter was to notify Plaintiffs that ANDA No. 91-465 included a certification under 21 U.S.C. § 355(j)(2)(a)(vii)(IV) ("Paragraph IV Certification") that the claims of the patents-in-suit would not be infringed by the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Defendants' product.

42. Attached to the July 27, 2009 letter was a "Detailed Statement" of the factual and legal basis for Defendant Sandoz Inc.'s opinion that the patents-in-suit would not be infringed by the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of the product described in ANDA 91-465. The Detailed Statement alleged that the patents-in-suit were invalid and therefore not infringed by the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Defendants' product.

43. On information and belief, Defendant Sandoz Inc. and/or Defendant Sandoz Canada Inc. are or will be involved in the importation into the United States of Sandoz Inc.'s generic equivalent to Precedex™.

44. On information and belief, Defendant Sandoz International GmbH and/or Defendant Sandoz Canada Inc. knowingly encouraged, directed, and actively induced Defendant Sandoz Inc. to prepare and file ANDA No. 91-465 with a Paragraph IV Certification.

45. On information or belief, Defendants were necessarily aware of the patents-in-suit when Defendant Sandoz Inc. filed ANDA No. 91-465 with a Paragraph IV Certification.

46. Hospira received the July 27, 2009 letter on July 28, 2009. Orion received the July 27, 2009 letter on July 29, 2009. Plaintiffs commenced this action within 45 days of the date they received Defendant Sandoz Inc.'s notice of the Paragraph IV Certification filing with the FDA.

FIRST CLAIM FOR RELIEF

(Infringement of the '214 Patent by Defendants)

47. Paragraphs 1 through 46 are incorporated herein as set forth above.

48. Defendants Sandoz Inc. and Sandoz Canada Inc. submitted ANDA No. 91-465 with a Paragraph IV Certification to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of dexmedetomidine hydrochloride injection 100 mcg base/ml prior to the expiration of the '214 patent. By submitting this ANDA, Defendants Sandoz Inc. and Sandoz Canada Inc. committed an act of infringement under 35 U.S.C. § 271(e)(2).

49. Moreover, Defendants' commercial manufacture, use, sale, offer for sale, and/or importation into the United States of the proposed generic dexmedetomidine hydrochloride product described in ANDA 91-465 would infringe the '214 patent under 35 U.S.C. § 271(a), (b), and/or (c).

50. Defendants were aware of the existence of the '214 patent prior to the filing of ANDA No. 91-465, but took such action knowing it would constitute infringement of the '214 patent.

51. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '214 patent.

SECOND CLAIM FOR RELIEF

(Infringement of the '867 Patent by Defendants)

52. Paragraphs 1 through 51 are incorporated herein as set forth above.

53. Defendants Sandoz Inc. and Sandoz Canada Inc. submitted ANDA No. 91-465 with a Paragraph IV Certification to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of dexmedetomidine hydrochloride injection 100 mcg base/ml prior to the expiration of the '867 patent. By submitting this ANDA, Defendants Sandoz Inc. and Sandoz Canada Inc. committed an act of infringement under 35 U.S.C. § 271(e)(2).

54. Moreover, Defendants' commercial manufacture, use, sale, offer for sale, and/or importation into the United States of the proposed generic dexmedetomidine hydrochloride product described in ANDA 91-465 would infringe the '867 patent under 35 U.S.C. § 271(a), (b), and/or (c).

55. Defendants' actions and conduct will encourage direct infringement of the '867 patent by others.

56. Defendants were aware of the existence of the '867 patent prior to the filing of ANDA No. 91-465, but took such action knowing it would constitute infringement of the '867 patent.

57. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '867 patent.

THIRD CLAIM FOR RELIEF

(Inducement of Infringement of the Patents-in-Suit by Sandoz International GmbH and Sandoz Canada Inc.)

58. Paragraphs 1 through 57 are incorporated herein as set forth above.

59. Through the conduct alleged above, Defendant Sandoz International GmbH has knowingly and actively induced Defendant Sandoz Inc. to infringe and continue to infringe one or more claims of the patents-in-suit.

60. Through the conduct alleged above, Defendant Sandoz Canada Inc. has knowingly and actively induced Defendant Sandoz Inc. to infringe and continue to infringe one or more claims of the patents-in-suit.

61. By reason of Defendants Sandoz International GmbH's and Sandoz Canada Inc.'s inducement of Defendant Sandoz Inc.'s direct infringement of the patents-in-suit, Defendants Sandoz International GmbH and Sandoz Canada Inc. have caused and continue to cause irreparable harm to Plaintiffs.

62. On information and belief, Defendants Sandoz International GmbH's and Sandoz Canada Inc.'s inducement of Defendants Sandoz Inc.'s direct infringement of patents-in-suit will continue unless enjoined by this Court.

63. Plaintiffs have no adequate remedy at law for Defendants Sandoz International GmbH's and Sandoz Canada Inc.'s inducement of Sandoz Inc.'s direct infringement of patents-in-suit.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. An order decreeing that Defendants have infringed the patents-in-suit;

B. An order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of ANDA No. 91-465 be no earlier than the expiration date of the last to expire of the patents-in-suit including any applicable extensions;

C. A preliminary and permanent injunction pursuant to 35 U.S.C. § 271(e)(4) restraining and enjoining Defendants, their officers, agents, attorneys, and employees and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale within the United States, and/or importation into the United States of the generic dexmedetomidine hydrochloride product described in ANDA No. 91-465 or any other ANDA not colorably different from ANDA No. 91-465 until the expiration of the last to expire of the patents-in-suit including any applicable extensions;

D. A declaration that this case is exceptional and an award of attorneys' fees under 35 U.S.C. § 285; and

E. Such other and further relief as the Court may deem just and proper.

Dated: May 17, 2010

CONNELL FOLEY LLP
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LOCAL CIVIL RULE 11.2 CERTIFICATION

I certify that, to the best of my knowledge, the matter in controversy is not the subject of any other pending or anticipated litigation in any court or arbitration proceeding, nor are there any non-parties known to Plaintiffs that should be joined to this action. In addition, I recognize a continuing obligation during the course of this litigation to file and to serve on all other parties and with the Court an amended certification if there is a change in the facts stated in this original certification.

Dated: May 17, 2010

s/Liza M. Walsh
Liza M. Walsh

LOCAL CIVIL RULE 201.1 CERTIFICATION

I hereby certify that the above-captioned matter is not subject to compulsory arbitration in that declaratory and injunctive relief is sought.

Dated: May 17, 2010

s/Liza M. Walsh
Liza M. Walsh

EXHIBIT A

United States Patent [19]

Karjalainen et al.

[11] **Patent Number: 4,910,214**

[45] **Date of Patent: Mar. 20, 1990**

[54] **OPTICAL ISOMER OF AN IMIDAZOLE DERIVATIVE MEDETOMIDINE AS AN ALPHA-2-RECEPTOR AGONIST**

[75] Inventors: **Arto J. Karjalainen**, Oulu; **Raimo E. Virtanen**, Rusko; **Eino J. Savolainen**, Oulu, all of Finland

[73] Assignee: **Farmos Yhtyma Oy**, Turku, Finland

[21] Appl. No.: **219,637**

[22] Filed: **Jul. 15, 1988**

[30] **Foreign Application Priority Data**

Jul. 16, 1987 [GB] United Kingdom 8716803

[51] Int. Cl.[4] **A61K 31/415; C07D 233/58**

[52] U.S. Cl. **514/396; 548/335**

[58] Field of Search 548/335; 514/396

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,544,664 10/1985 Karjalainen et al. 514/400

FOREIGN PATENT DOCUMENTS

0024829 3/1981 European Pat. Off. .
0058047 8/1982 European Pat. Off. .
0072615 2/1983 European Pat. Off. .
02114528 3/1987 European Pat. Off. .

OTHER PUBLICATIONS

Chemical Abstracts, 105: 183977c (1986) [JPN. Kokai 61, 134, 314, Farmos, 6/21/86].

Noller, C., *Chemistry of Carbon Compounds*, 2nd Ed., W. B. Saunders, Philadelphia, 1957, pp. 341–344.

Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—Armstrong, Nikaido, Marmelstein, Kubovcik & Murray

[57] **ABSTRACT**

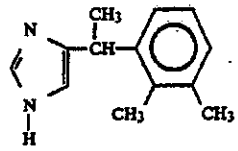
The separated d and l enantiomers of medetomidine and their salts are selective and potent α_2-receptor agonists.

4 Claims, No Drawings

OPTICAL ISOMER OF AN IMIDAZOLE DERIVATIVE MEDETOMIDINE AS AN ALPHA-2-RECEPTOR AGONIST

This invention relates to optical isomers of imidazole derivatives and to their preparation.

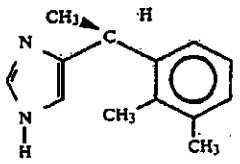
Medetomidine which has the formula:



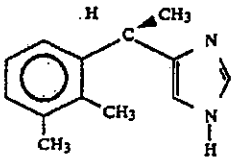
I

is known as a selective and potent α_2-receptor agonist. It has been described, e.g. in European Patent Publication No. 72615, as an antihypertensive agent and in the European Patent Publication No. 187471 as a veterinary sedative-analgesic agent.

The present invention provides, as new compounds, the optically active d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. These compounds may be represented by the formulae:



II



III

According to a feature of the invention, racemic medetomidine is separated into the enantiomers II and III by conversion of the racemate into a mixture of diastereoisomers and separating the latter by fractional crystallization. Since medetomidine is a base, it may be converted into a diastereoisomer salt mixture by reaction with an optically active acid such as (+)-tartaric acid. Other useful optically active acids are, e.g., (−)-malic acid, (−)-mandelic acid and (+)-camphor-10-sulfonic acid. (+)-Tartaric acid is especially useful for the resolution. The separation of the diastereisomers is performed by repeated crystallizing from an alcohol such as methanol or ethanol or a mixture of them.

Once the diastereoisomers have been separated the acid addition salts can be converted back to the free bases by making their aqueous solutions alkaline with sodium hydroxide and by extracting the liberated base in an appropriate organic solvent such as methylene chloride.

The d- and l-enantiomers of medetomidine react with organic and inorganic acids to form the corresponding acid addition salts, which have the same therapeutic activities as the bases. They can thus form many pharmaceutically usable acid addition salts, as, for instance, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates and the like.

The d- and l-enantiomers of medetomidine are selective and potent α_2-receptor agonists.

Adrenergic receptors are physiologically important binding sites which are specific to noradrenaline and adrenaline and located on the surface of the cell membrane. The adrenoceptors of the sympathetic nervous system have been classified into two different subtypes, alpha-(α) and beta-(β) receptors, which can be further divided into two subgroups, viz α_1 and α_2 and β_1 and β_2. Of these receptor types, β_1, β_2 and α_1 are mainly located post-synaptically on the surface of, e.g., smooth muscle and thus mediate, e.g., smooth muscle contraction or relaxation; whereas α_2 receptors are mainly located presynaptically on the terminals of noradrenergic nerves. If α_2-receptors are stimulated by noradrenaline under physiological conditions noradrenaline release is blocked, i.e. there is a negative feed-back phenomenon. This negative feed-back phenomenon may also be induced by certain synthetic α_2-agonists like medetomidine and some of its near derivatives.

In animal experiments, the d- and l- enantiomers of the present invention and especially the d-enantiomer, have proved to possess highly enhanced α_2-selectivity and potency compared to the racemic mixture (i.e. medetomidine). The d-enantiomer can be expected to be of value, e.g., as a sedative-analgesic, anxiolytic or antihypertensive agent. Furthermore, it can be used as a pharmacological tool in the study of the physiology and pharmacology of α_2-adrenoceptors.

The pharmacological activity of the compounds of the invention was determined as follows:

1. ALPHA-2 AGONISM IN VITRO

α_2-agonism was determined by means of isolated, electrically stimulated mouse was deferens preparation (Marshall et al., Br. J. Pharmac. 62, 147–151, 1978). In this model, an α_2-agonist is able to block electrically induced muscular contractions by activating the presynaptic α_2-adrenoceptors and thus diminishing the secretion on the motor transmitter. Known α_2-agonists like detomidine, medetomidine and clonidine were used as reference substances. Results are shown in Table 1, where the α_2-agonist effect is presented as the pD_2-value (negative logarith of the molar concentration of the compound producing 50 percent of maximal inhibition.)

TABLE 1

Compound	α_2-agonism in vitro (mouse vas deferens), pD_2
d-enantiomer	9.3
l-enantiomer	6.0 (partial agonist)
medetomidine	9.0
detomidine	8.5
clonidine	8.5

These results show that the α_2-agonist activity of medetomidine is limited to the d-enantiomer. The d-enantiomer shows an enhanced α_2-agonist activity compared to the outer agents studied.

2. α_2/α_1-SELECTIVITY IN VITRO

The selectivity of the d-enantiomer as an α_2-agonist was studied in receptor binding experiments using rat brain membranes. The ability of the d-isomer and the reference compounds to compete with ^{3}H-clonidine

(for α_2-receptors) and ^{3}H-prazosin (for α_1-receptors) was studied essentially as described by Virtanen and Nyman in Eur. J. Pharmac. 108, 163–9, 1985. Results of the test are presented in Table 2, where the ability of the studied agents to compete with ^{3}H-clonidine and ^{3}H-prazosin binding is expressed as the IC_{50}-value (molar concentration of the competing ligand needed to displace 50 percent of the radioactive ligand).

TABLE 2

Compound	^{3}H-clonidine displacement IC_{50}, nM	^{3}H-prazosin displacement IC_{50}, nM	α_2/α_1-selectivity
d-enantiomer	1.2	55019	45849
l-enantiomer	46	189975	4129
medetomidine	3.3	16700	5060
detomidine	3.7	242	65
clonidine	6.4	6200	969

The results show that the d-enantiomer is an extremely selective α_2-agonist compared to medetomidine and the other reference compounds.

3. SEDATIVE ANALYGESIC EFFECTS

The sedative-analgesic properties of the compounds were studied in the spontaneous motility and writhing-test in the mouse. Spontaneous motility of mice and rats was measured using the Animex-activity meter. The test compounds were administered i.p. 30 minutes before the measuring periods of two minutes. In the writhing test the compounds studied and saline were administered s.c. to rats, and 45 min. later 1 ml of 1% acetic acid was administered i.p. The number of writhes was recorded in the following 25 min. period (Koster et al., Fred. Proc. 18: 412, 1959). Results are shown in Tables 3 and 4.

TABLE 3

Compound	ED_{50} -values of the studied compounds in reducing spontaneous motility in mice ED_{50} (mg/kg s.c.)
d-enantiomer	0.02
l-enantiomer	>10
medetomidine	0.05
detomidine	0.3
clonidine	0.3

TABLE 4

Compound	ED_{50}-values of the studied compounds in acetic acid-induced writhing test in mice ED_{50} (mg/kg s.c.)
d-enantiomer	0.01
l-enantiomer	>10
medetomidine	0.02
detomidine	0.02
clonidine	0.03

These results shown that the d-enantiomer has an enhanced sedative/analgesic property compared to the racemic mixture (medetomidine) and other reference compounds. The sedative/analgesic effects of medetomidine are confined to the d-enantiomer.

4. ANXIOLYTIC EFFECTS

The anxiolytic effects of the compounds were studied using a method described by Handley and Mithoni: Naunyn-Schmiedeb, Arch. Pharmacol. 327, 1–5, 1984. In this test the manner of exploration of open and enclosed arms in an elevated t-maze by a rat is examined. It has been shown that anxiolytic drugs increase the relative exploration of open arms. A rat is placed in the center of the t-maze and the number of open and enclosed entries is recorded during 5 minutes. Results obtained are shown in Table 5.

TABLE 5

Drug/dose, mg/kg	Mean number of entries (n = 6) open	closed	total	open/total
NaCl	3.4	8.6	12.0	0.28
d-enantiomer				
0.0003	4.8	10.6	14.0	0.20
0.001	3.2	10.6	13.8	0.23
0.003	4.0	9.5	13.5	0.29
0.01	5.8	8.8	14.6	0.39
0.03	2.5	3.0	5.5	0.45
diazepam				
1	5.2	10.5	15.7	0.33

The results show that the d-enantiomer has an anxiolytic profile in the elevated t-maze test.

It is well known that anxiety states connected to withdrawal symptoms are due to noradrenergic hyperactivity. Therefore such symptoms can be successfully treated with drugs reducing the level of noradrenaline, e.g. clonidine. Experiments in the rat indicate that the d-enantiomer is able to reduce noradrenaline release and thus sympathetic tone both in the central and peripheral nervous systems. This has clearly been demonstrated by measuring CSF-concentrations of MHPG-SO_4 (the principal metabolite of central noradrenaline) in the rat after d-enantiomer administration. The results are shown in Table 6.

TABLE 6

d-enantiomer dose µg/kg	CSF MHPG-SO_4 (% of control) (4 h after d-enantiomer adm.)
0	100
3	−10
10	−20
30	−30
100	−65

5. ANTIHYPERTENSIVE EFFECTS

The antihypertensive properties of the compounds of the invention have been studied as follows: Sprague-Dawley rats of normal weight were first anesthetized with urethane. After this, the femoral artery was connected by a polyethylene tube to a blood pressure transducer. The test substance was then injected into the femoral vein and the blood pressure and the pulse frequency were registered with a recorder. Results are shown in Table 7.

TABLE 7

Dose, mg/kg	Antihypertensive effects of the d-enantiomer in anesthetized rats Decrease in BP, %	Decrease in heart rate, %
0.001	−8	−21
0.003	−23	−40
0.01	−43	−47
0.03	−45	−48
0.1	−45	−50

The results show that the d-enantiomer possesses clear anti-hypertensive and bradycardia effects.

The d- and l-enantiomers, and their non-toxic, pharmaceutically acceptable acid addition salts or mixtures thereof may be administered parenterally, intravenously or orally. Typically, an effective amount of the compound is combined with a suitable pharmaceutical car-

rier. As used herein, the term "effective amount" encompasses those amounts which yield the desired activity without causing adverse side-effects. The precise amount employed in a particular situation is dependent upon numerous factors such as method of administration, type of mammal, condition for which the derivative is administered, etc. and of course the structure of the derivative.

The pharmaceutical carriers which are typically employed with the compounds of the present invention may be solid or liquid and are generally selected with the planned manner of administration in mind. Thus, for example, solid carriers include lactose, sucrose, gelatin and agar, while liquid carriers include water, syrup, peanut oil and olive oil. Other suitable carriers are well known to those skilled in the art of pharmaceutical formulations. The combination of the derivative and the carrier may be fashioned into numerous acceptable forms, such as tablets, capsules, suppositories, solutions, emulsions, and powders.

The following Example illustrates the separation of the new enantiomers.

EXAMPLE

14 g of medetomidine (base) were dissolved in 50 ml of methanol. 10.5 g of (+)-tartaric acid were dissolved in 50 ml of methanol. The solutions were mixed and the solvent was evaporated to a volume of 50 ml. The mixture was put into an ice bath and 9 g of white precipitate was obtained. The precipitate was suspended in 25 ml of ethanol, the mixture was kept in ultrasonic sound for 14 min and filtered. The precipitate was dissolved in a mixture of 20 ml abs. ethanol and 60 ml methanol by heating on a steam bath. After cooling, 5 g of precipitate (degree of rotation +55°) was obtained. After recrystallization from 60 ml of methanol, 4.1 g of product was obtained, degree of rotation +60°. Recrystallization was repeated until the degree of rotation did not increase any longer. The d-enantiomer tartrate was dissolved in water, the solution was made alkaline and the d-enantiomer was dissolved in an organic solvent e.g. dichlormethane or diethyl ether. The degree of rotation of the d-enantiomer base was +75°.

The l-enantiomers may be isolated from the mother liquors.

We claim:

1. The d enantiomer of medetomidine or a non-toxic pharmaceutically acceptable acid addition salt thereof.

2. A pharmaceutical composition suitable for use in a method of sedation/analgesia or treatment of anxiety or hypertension comprising the d-enantiomer of medetomidine or a non-toxic pharmaceutically acceptable acid addition salt thereof in an amount sufficient to produce the desired effect in association with a pharmaceutical carrier.

3. A method of sedation/analgesia or treatment of anxiety or hypertension by administration to a subject of an effective amount of an enantiomer according to claim 1.

4. A method of sedation/analgesia or treatment of anxiety or hypertension by administration to a subject of an effective amount of a composition according to claim 2.

* * * * *

EXHIBIT B

US006716867B1

(12) **United States Patent**
Aantaa et al.

(10) **Patent No.: US 6,716,867 B1**
(45) **Date of Patent: Apr. 6, 2004**

(54) **USE OF DEXMEDETOMIDINE FOR ICU SEDATION**

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§ 371 (c)(1),
(2), (4) Date: **Dec. 6, 2000**

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PCT Pub. Date: **Oct. 7, 1999**

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(51) **Int. Cl.**[7] **A61K 31/415**
(52) **U.S. Cl.** **514/396**
(58) **Field of Search** 514/396

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(57) **ABSTRACT**

The present invention relates to a method of sedating a patient while in the intensive care unit comprising administering dexmedetomidine of a pharmaceutically acceptable salt thereof to the patient, wherein the patient remains arousable and orientated.

12 Claims, 2 Drawing Sheets

CLINICAL SCORE	LEVEL OF SEDATION ACHIEVED
1	PATIENT ANXIOUS, AGITATED OR RESTLESS
2	PATIENT CO-OPERATIVE, ORIENTED AND TRANQUIL
3	PATIENT RESPONDS TO COMMANDS
4	ASLEEP BUT WITH BRISK RESPONSE TO LIGHT GLABELLAR TAP OR LOUD AUDITORY STIMULUS
5	ASLEEP, SLUGGISH RESPONSE TO LIGHT GLABELLAR TAP OR LOUD AUDITORY STIMULUS
6	ASLEEP, NO RESPONSE

FIG. 1

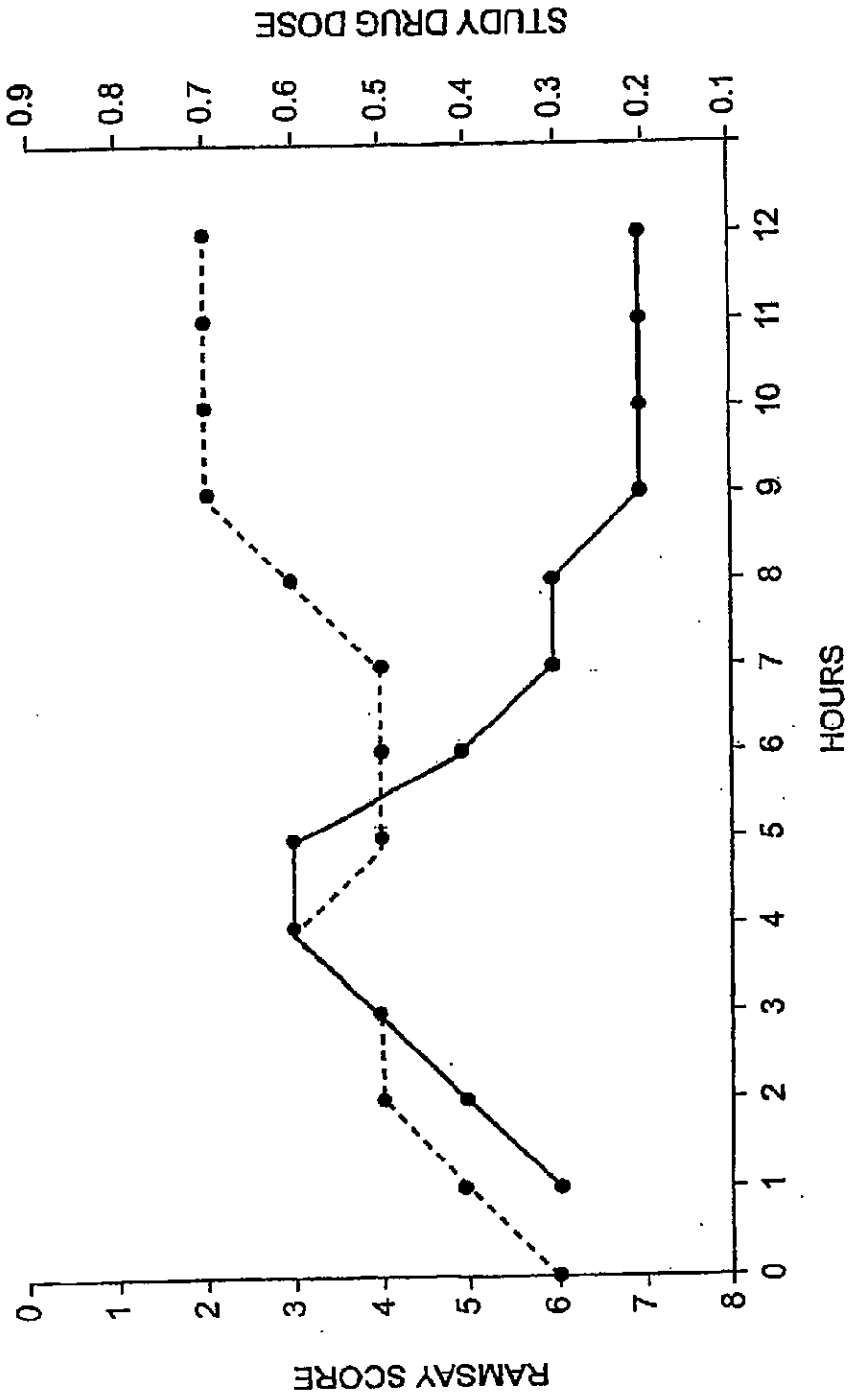

STUDY DRUG DOSE
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
5
6
7
8
9
10
11
12
HOURS
RAMSAY SCORE
0
1
2
3
4
5
6
7
8

FIG. 2

USE OF DEXMEDETOMIDINE FOR ICU SEDATION

This application is a national stage filing of PCT International Application No. PCT/F199/00266, filed on Mar. 31, 1999, which claims priority to U.S. Provisional Application Ser. No. 60/080,287, filed on Apr. 1, 1998, and which also claims priority to U.S. Provisional Application Ser. No. 60/110,944, filed on Dec. 4, 1998.

BACKGROUND OF THE INVENTION

The present invention relates to the use of dexmedetomidine or a pharmaceutically acceptable salt thereof in intensive care unit (ICU) sedation. In addition to the actual sedation of a patient in the ICU, the word sedation in the ICU context also includes the treatment of conditions that affect patient comfort, such as pain and anxiety. Also, the word intensive care unit includes any setting that provides intensive care. Accordingly, the present invention relates to a method of sedating a patient while in the ICU by administering dexmedetomidine or a pharmaceutically acceptable salt thereof. Particularly, the present invention relates to a method of sedating a patient while in the ICU by administering dexmedetomidine or a pharmaceutically acceptable salt thereof, wherein dexmedetomidine is essentially the sole active agent or the sole active agent administered for this purpose. The present invention also relates to the use of dexmedetomidine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for intensive care unit sedation.

Patients recovering from an episode of critical illness have reported factors they found most distressing during their ICU stay (Gibbons, C. R., et al., Clin. Intensive Care 4 (1993) 222–225). The most consistently unpleasant memories are anxiety, pain, fatigue, weakness, thirst, the presence of various catheters, and minor procedures such as physiotherapy. The aim of ICU sedation is to ensure that the patient is comfortable, relaxed, and tolerates uncomfortable procedures such as placement of iv-lines or other catheters, but is still arousable.

At the moment, there is no universally accepted sedative regimen for critically ill patients. Thus, these patients receive a variety of drugs during their stay in an ICU, often receiving the variety of drugs concurrently The agents used most commonly are given to achieve patient comfort. Various drugs are administered to produce anxiolysis (benzodiazepines), amnesia (benzodiazepines), analgesia (opioids), antidepression (antidepressants/benzodiazepines), muscle relaxation, sleep (barbiturates, benzodiazepines, propofol) and anaesthesia (propofol, barbiturates, volatile anesthetics) for unpleasant procedures. These agents are cumulatively called sedatives in the context of ICU sedation, though sedation also includes the treatment of conditions that affect patient comfort, such as pain and anxiety, and many of the drugs mentioned above are not considered sedatives outside the context of ICU sedation.

The presently available sedative agents are associated with such adverse effects as prolonged sedation or oversedation (propofol and especially poor metabolizers of midazolam), prolonged weaning (midazolam), respiratory depression (benzodiazepines, propofol, and opioids), hypotension (propofol bolus dosing), bradycardia, ileus or decreased gastrointestinal motility (opioids), immunosuppression (volatile anaesthetics and nitrous oxide), renal function impairment, hepatotoxicity (barbiturates), tolerance (midazolam, propofol), hyperlipidemia (propofol),

increased infections (propofol), lack of orientation and cooperation (midazolam, opioids, and propofol), and potential abuse (midazolam, opioids, and propofol).

In addition to the adverse effects of every individual sedative agent, the combination of these agents (polypharmacy) may cause adverse effects. For example, the agents may act synergistically, which is not predictable; the toxicity of the agents may be additive; and the pharmacokinetics of each agent may be altered in an unpredictable fashion. In addition, the possibility of allergic reactions increases with the use of more than one agent. Furthermore, these adverse effects might necessitate the use of additional agents to treat the adverse effects, and the additional agents themselves may have adverse effects.

The preferred level of sedation for critically ill patients has changed considerably in recent years. Today, most intensive care doctors in the ICU prefer their patients to be asleep but easily arousable, and the level of sedation is now tailored towards the patient's individual requirements. Muscle relaxants are seldom used during intensive care. As cardiovascular stability is also desired in this often high-risk patient population, hemodynamically active agents are often needed for adequate hemodynamic control despite sufficient sedation.

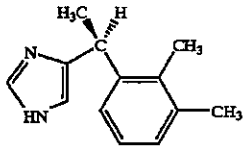
α_2-adrenoceptor agonists are being evaluated in general anaesthetic practice because of their sympatholytic, sedative, anaesthetic, and hemodynamic stabilizing effects. Tryba et al. discussed the usefulness of α_2-agonists in situations where patients with withdrawal symptoms are treated in the ICU (Tryba et al., Drugs 45 (3) (1993), 338–352). The only α_2-agonist mentioned was clonidine, which was used in conjunction with opioids, benzodiazepines, ketamine, and neuroleptics. Tryba et al. suggest that clonidine may be useful in ICU patients with withdrawal symptoms, but Tryba et al. only briefly mention the use of clonidine for ICU sedation. Furthermore, Tryba et al. only mention clonidine as a supplement to other sedatives for ICU sedation.

According to Tryba et al., clonidine has its limitations in sedating critically ill patients mainly because of its unpredictable hemodynamic effects, i.e., bradycardia and hypotension, so that it must be titrated for each individual patient. Long term treatment of critically ill patients with clonidine has been reported to be associated with such rebound effects as tachycardia and hypertension.

α_2-agonists are not presently used by themselves in ICU sedation. Further, α_2-agonists are not generally used in ICU sedation even in conjunction with other sedative agents. Only clonidine has been evaluated for use in ICU sedation, and then only in conjunction with opioids, benzodiazepines, ketamine, and neuroleptics. Further, administration of clonidine as essentially the sole active agent or the sole active agent to a patient in the ICU to achieve sedation has not been disclosed to the best of applicants' knowledge.

An ideal sedative agent for a critically ill patient should provide sedation at easily determined doses with ready arousability together with hemodynamic stabilizing effects. Further, it should be an anxiolytic and an analgesic, and should prevent nausea, vomiting, and shivering. It should not cause respiratory depression. Preferably, an ideal sedative agent should be used by itself in ICU sedation to avoid the dangers of polypharmacy.

Dexmedetomidine, or (+)-(S)-4-[1-(2,3-dimethylphenyl) ethyl]-1H-imidazole, has the following formula:



Dexmedetomidine is described in U.S. Pat. No. 4,910,214 as an α_2-receptor 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. U.S. Pat. No. 5,304,569 discusses the use of dexmedetomidine in glaucoma. U.S. Pat. No. 5,712,301 discusses the use of dexmedetomidine for preventing neurodegeneration caused by ethanol consumption.

Medetomidine, which is the racemic mixture of dexmedetomidine and levomedetomidine, is known as a selective and potent α_2-agonist and has been described in U.S. Pat. No. 4,544,664 as an antihypertensive agent and in U.S. Pat. No. 4,670,455 as a veterinary sedative-analgesic agent.

In U.S. Pat. Nos. 4,544,664 and 4,910,214, parenteral, intravenous, and oral ways of administration are discussed. U.S. Pat. No. 4,670,455 describes intramuscular and intravenous administration. U.S. Pat. Nos. 5,124,157 and 5,217,718 describe a method and device for administering dexmedetomidine through the skin. U.S. Pat. No. 5,712,301 states that dexmedetomidine can be administered transmucosally.

The U.S. Patents discussed herein are specifically incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

It has been unexpectedly found that dexmedetomidine or a pharmaceutically acceptable salt thereof is an ideal sedative agent to be administered to a patient in the ICU to achieve patient comfort. Accordingly, an object of the invention is to provide a method of sedating a patient while in the ICU that comprises administering dexmedetomidine or a pharmaceutically acceptable salt thereof for a time sufficient to give the desired therapeutic effect.

It should be noted that the method for sedating a patient in the ICU encompasses all of the potential ICU uses of dexmedetomidine and a pharmaceutically acceptable salt thereof, including all potential uses that derive from their activity as α_2-agonists, e.g., their use as hypotensive agents, anxiolytics, analgesics, sedatives, and the like. It should also be noted that the word intensive care unit encompasses any setting that provides intensive care.

Additional objects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

In one aspect, the invention relates to a method of sedating a patient while in the ICU by administering dexmedetomidine or a pharmaceutically acceptable salt thereof, wherein dexmedetomidine is essentially the sole active agent or the sole active agent. The method is premised on the discovery that essentially only dexinedetomidine or a pharmaceutically acceptable salt thereof need to be administered to a patient in the ICU to achieve sedation and patient comfort. No additional sedative agents are required.

In a further aspect, the invention relates to a use of dexmedetomidine or a pharmaceutically acceptable salt thereof in ICU sedation.

A further aspect of the invention relates to a use of dexmedetomidine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for ICU sedation.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the Ramsay Scale that was developed for the assessment of sedation in experimental subjects. In this system, the level of wakefulness is scored on a scale of 1–6 (Ramsey Sedation Score) based on progressive loss of responsiveness to stimuli ranging from auditory to deep painful stimuli.

FIG. 2 shows the dosing period from the Phase III dexmedetomidine study described in Example 3, case No. 13. The dotted line signifies Ramsay Sedation Score fluctuations and the solid line signifies dexmedetomidine dose adjustments.

DETAILED DESCRIPTION OF THE INVENTION

Applicants have surprisingly discovered that dexmedetomidine or a pharmaceutically acceptable salt thereof is an ideal agent to be administered to a patient in the ICU for achieving sedation and patient comfort. Particularly, it has been found that dexmedetomidine or a pharmaceutically acceptable salt thereof can be essentially the sole active agent or the sole active agent administered to a patient in the ICU in order to sedate the patient.

The method for sedating a patient in the ICU encompasses all of the potential ICU uses of dexmedetomidine and a pharmaceutically acceptable salt thereof, including all potential uses that derive from their activity as α_2-agonists, e.g., their use as hypotensive agents, anxiolytics, analgesics, sedatives, and the like.

The word intensive care unit encompasses any setting that provides intensive care. The word patient is intended to include both human and animal patients. Preferably, the animal patient is a mammal, especially a dog, a cat, a horse, or a cow.

The quality of the sedation in the ICU achieved by administering dexmedetomidine is unique. Patients sedated by dexmedetomidine or a pharmaceutically acceptable salt thereof are arousable and oriented, which makes the treatment of the patient easier. The patients can be awakened and they are able to respond to questions. They are aware, but not anxious, and tolerate an endotracheal tube well. Should a deeper level of sedation or more sedation be required or desired, an increase in dexmedetomidine dose smoothly transits the patient into a deeper level of sedation. Dexmedetomidine does not have adverse effects associated with other sedative agents, such as, respiratory depression, nausea, prolonged sedation, ileus or decreased gastrointestinal motility, or immunosuppression. Lack of respiratory depression should allow dexmedetomidine to be used also for non-ventilated, critically ill patients who require sedation, anxiolysis, analgesia, and hemodynamic stability yet must remain oriented and easily aroused. In addition, it is water soluble and, thus, does not increase the lipid load in

patients sedated for long periods of time. A predictable pharmacological response can be achieved by administering dexmedetomidine or a pharmaceutically acceptable salt thereof to a patient in the ICU.

Dexmedetomidine or a pharmaceutically acceptable salt thereof can be administered perorally, transmucosally, transdermally, intravenously or intramuscularly. One skilled in the art would recognize the doses and dosage forms suitable in the method of the present invention. The precise amount of the drug administered according to the invention is dependent on numerous factors, such as the general condition of the patient, the condition to be treated, the desired duration of use, the route of administration, the type of mammal, etc. The dose range of dexmedetomidine can be described as target plasma concentrations. The plasma concentration range anticipated to provide sedation in the patient population in the ICU varies between 0.1–2 ng/ml depending on the desired level of sedation and the general condition of the patient. These plasma concentrations can be achieved by intravenous administration by using a bolus dose and continuing it by a steady maintenance infusion. For example, the dose range for the bolus to achieve the forementioned plasma concentration range in a human is about 0.2–2 μg/kg, preferably about 0.5–2 μg/kg, more preferably 1.0 μg/kg, to be administered in about 10 minutes or slower, followed by a maintenance dose of about 0.1–2.0 μg/kg/h, preferably about 0.2–0.7 μg/kg/h, more preferably about 0.4–0.7 μg/kg/h. The time period for administering dexmedetomidine or a pharmaceutically acceptable salt thereof depends on the the desired duration of use.

The chemical form for dexynedetomidine can be the free base or an acid addition salt. Such acid addition salts may be formed, for example, with inorganic acids, such as, hydrochloric acid, hydrobromic acid, sulfiric 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, malcic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The invention will be further clarified by the following example, which is intended to be purely exemplary of the invention.

EXAMPLE 1

The efficacy, safety and titratability of dexmedetomidine in postoperative coronary artery bypass graft(s) patients (CABG), requiring sedation in the ICU was studied. The patients were intubated for 8–24 hours. All patients were administered dexmedetomidine within 1 hour of admission to the ICU, and dexmedetomidine infusion was continued until 6 hours after extubation. Dexmedetomidine was used in the form of an HCl salt (100 μg/ml, base) in 0.9% sodium chloride solution, and it was administered as a two-stage infusion (a loading dose followed by a maintenance infusion) utilizing standard syringe pump and iv administration sets.

12 patients were selected and divided into two groups. The first 6 patients were administered a loading dose of 6 μg/kg/h of dexmedetomidine over a 10-minute period, followed by a maintenance infusion of 0.2 μg/kg/h. The second group of 6 patients were initially administered a loading dose of 6.0 μg/kg/h of dexmedetomidine over a 10 minute period, followed by a maintenance infusion of 0.4 μg/kg/h. The infusion rate in both groups was maintained between a range of 0.2 to 0.7 μg/kg/h. After the clinical effects of sedation became evident (approximately within 15 to 30 minutes) the maintenance rate of infusion could be adjusted in increments of 0.1 μg/kg/h or higher to achieve and maintain a Ramsey Sedation Score level of 3 or higher (see FIG. 1).

Vital signs, adverse events, and sedation scores were recorded during the study. The patients did not receive any of the following medications during the administration of dexmedetomidine: sedating agents, neuromuscular blocking agents except for insertation of the endotracheal tube, and epidural or spinal analgesic/anaesthetic agents. Two patients required morphine for pain. One patient had two serious adverse events: circulatory failure and myocardial infarction. The myocardial infarction, due to incomplete revascularization, led to death 13 days after the study drug infusion had been discontinued. The myocardial infarction had little or no temporal relationship to dexmedetomidine. In fact, incomplete revascularization is one of the most common adverse events after a CABG operation, and it sometimes leads to death.

During the administration of dexmedetomidine, the blood pressure and heart rate variability were decreased, meaning more stable and predictable hemodynamics without the need for pharmacological interventions to either treat high blood pressure or heart rate, e.g., with beta-blockers, or to increase sedation/anxiolysis with benzodiazepins or propofol. In conclusion, the patients were conveniently sedated, hemodynamically stable, and remained easily arousable for control of subjective well being with only one pharmaceutical, dexmedetomidine.

The example shows that dexmedetomidine is an ideal agent for sedating a patient in the ICU, providing a unique quality of sedation and patient comfort.

EXAMPLE 2

A double-blind, randomized, placebo-controlled study was conducted to evaluate the efficacy, safety, and titratability of dexmedetomidine in mechanically ventilated patients requiring sedation in the ICU. The study was conducted in postoperative CABG patients requiring sedation in the ICU. Twelve adult postoperative CABG patients requiring mechanical ventilation in the ICU who met the study selection criteria were eligible for participation.

The selection criteria were as follows. The patients required sedation for mechanical ventilation for a minimum of 8 hours following surgery, followed by continued sedation for 6 hours after extubation. The patients were not to have been intubated longer than 24 hours to be evaluable for the test. The patients received only morphine for management for pain and received none of the following medications during study drug administration: sedating agents other than midazolam, neuromuscular blocking agents except for insertion of the endotrachael tube, epidural or spinal analgesic/anesthetic agents.

Safety was evaluated through the monitoring of adverse events, cardiac monitoring, laboratory tests, vital signs, oxygen saturation, and concomitant medications.

Twelve patients were randomly assigned to receive either dexmedetomidine or placebo with rescue treatment for sedation with midazolam, as clinically indicated. Patients randomized to dexmedetomidine were to receive a 10-minute loading dose of 6.0 μg/kg/h, followed by an initial maintenance infusion. The rate of maintenance infusion was 0.4 μg/kg/h. The maintenance rate of infusion could be titrated in increments of 0.1 μg/kg/h to achieve and maintain a Ramsey Sedation Score of 3 or higher. The range for the

maintenance infusion was to be kept between 0.2 and 0.7 μg/kg/h. Dexmedetomidine administration was to begin within one hour after admission to the ICU and continued until 6 hours after extubation. Dexmedetomidine was used in the form of an HCl salt (100 μg/ml, base) in 0.9% sodium chloride solution, and it was administered utilizing standard syringe pump and iv administration sets. The placebo was 0.9% sodium chloride solution administered the same way dexmedetomidine was administered.

The six dexmedetomidine-sedated patients remained adequately sedated and did not require any midazolam. Conversely, five of the six placebo-treated patients required the administration of midazolam to achieve sufficient (Ramsay Sedation Score≧3) levels of sedation (total mean midazolam mg/kg/h±SEM=0.018±0.005). The difference between the two treatment groups in mean total dose of midazolam received during the study was statistically significant (p=0.010). The overall level of sedation was comparable between the two groups, but the administration of dexmedetomidine resulted in stable Ramsey Sedation Scores, characterized by minimal variability over time, compared with intermittent sedation (Ramsey Sedation Score≧3) and agitation (Ramsey Sedation Score of 1) among placebo-treated patients.

Dexmedetomidine also demonstrated analgesic properties in this patient population, as measured by the total dose of morphine administered throughout the duration of the study. One of six dexmedetomidine-treated patients required morphine administration for management of pain compared to five of the six placebo-treated patients. The difference between the treatment groups in mean total dose of morphine was statistically significant (p=0.040).

In conclusion, patients treated with dexmedetomidine required significantly less midazolam for sedation or morphine for pain than did patients who received placebo. Sedation levels for dexmedetomidine-treated patients were more stable than those for placebo-treated patients who received midazolam. Dexmedetomidine was safe and well tolerated, and it produced no clinically apparent respiratory depression after cessation of assisted ventilation.

EXAMPLE 3

Two Phase III dexmedetomidine multicenter clinical trials (Trial 1 and Trial 2) have been conducted in ICU sedation in Europe and Canada. Each trial had two parts, i.e., an open-label part (Part I) and double-blind, randomized, placebo-controlled part (Part II). The trials were designed to evaluate the reduction in requirements for ICU sedation (as measured by administration of other sedative/analgesic agents) in patients receiving dexmedetomidine. The use of propofol and morphine for sedation and analgesia, respectively, was evaluated in one trial (Trial 1), and midazolam and morphine in the other trial (Trial 2). A total of 493 patients were enrolled and treated in Trial 1 and 438 patients were enrolled and treated in Trial 2.

In Part I of the trials patients were to be administered a 6.0 μg/kg/h loading dose of dexmedetomidine over a 10-minute period, followed by an initial maintenance infusion of 0.4 μg/kg/h. During Part II of the study, patients were randomly assigned to receive either placebo (0.9% sodium chloride solution) or dexmedetomidine. Dexmedetomidine was used as an HCl salt (100 mg/ml, base) in 0.9% sodium chloride solution, and it was administered utilizing standard syringe pump and iv administration sets. The dexmedetomidine dosing protocol was the same as in the Part I of the study. For both parts of the study, following the initial maintenance infusion, the rate of infusion could have been adjusted in increments of 0.1 μg/kg/h or higher. The infusion rate during intubation was to have been maintained in the range of 0.2 to 0.7 μg/kg/h in order to achieve and maintain a Ramsey Sedation Score of 3 or higher. Following extubation, the infusion rate was to be adjusted to achieve a Ramsay Sedation Score of 2 or higher.

During the 10-minute loading dose, additional medication was to be avoided, but propofol (0.2-mg/kg bolus) in Trial 1 and midazolam (1-mg bolus) in Trial 2 could be given if necessary. During dexmedetomidine infusion, rescue medications were limited to propofol (0.2 mg/kg IV boluses) in Trial 1 and midazolam (0.2-mg/kg IV boluses) in Trial 2 for sedation and morphine for pain (2-mg IV boluses). After extubation, paracetamol was to be permitted for pain as clinically indicated. Propofol and midazolam were to be given only after increasing the dexmedetomidine infusion rate. Dexmedetomidine administration in Parts I and II was to begin within 1 hour of admission to the ICU and to be continued for 6 hours after extubation to a maximum of 24 hours total study drug infusion. Patients were observed and assessed for an additional 24 hours after cessation of dexmedetomidine.

The conclusions from the Trials 1 and 2 are as follows. The patients treated with dexmedetomidine required significantly less propofol (Trial 1) or midazolam (Trial 2) for sedation or morphine for pain than patients who received placebo. The sedation levels for dexmedetomidine-treated patients were achieved more quickly than those for placebo-treated patients who received propofol or midazolam. Dexmedetomidine was safe and well tolerated: the adverse events and laboratory changes reported in these studies were to be expected in a postsurgical population.

During Trial 1, Part I three dexmedetomidine-treated patients died, and during Trial 1, Part II, three dexmedetomidine-treated patients died and one placebo-treated patient died. However, none of the adverse events leading to death were considered to be related to dexmedetomidine administration. No deaths occurred among dexmedetomidine-treated patients in Part I and Part II of Trial 2,but five placebo-treated patients died. Dexmedetomidine produced changes in systolic blood pressure, diastolic blood pressure, and heart rate consistent with the known pharmacological effect of α_2-agonists. Further, dexmedetomidine produced no clinically apparent respiratory depression after cessation of assisted ventilation.

The following 16 cases are from the above mentioned Part II of trials 1 and 2. The cases indicate that dexmedetomidine has analgesic properties and provides effective sedation and anxiolysis while allowing patients to remain oriented and communicative.

1. A 86-year-old female patient underwent abdominal resection due to a tumor in the colon. Surgery was performed with a short-acting analgesia (remifentanil). The patient was a non-smoker and had no cardiac history apart from elevated blood pressure. On arrival in the ICU, she required two doses each of morphine and midazolam. Dexmedetomidine was started at a loading dose of 6 μg/kg/h for 10 minutes and was maintained at a rate of 0.4 μg/kg/h for 30 minutes, followed by a mean dose of 0.5 μg/kg/h. The patient's Ramsay Sedation Score was 6 during the first hour, then decreased to 3 and, later, to 2. While receiving dexmedetomidine, the patient required only one dose of morphine 5 minutes before extubation. Extubation was performed at 6.5 hours and was uneventful.

2. A 66-year-old male patient underwent lobectomy of the right lung. The patient was formerly a heavy smoker (three packs a day) but had stopped 10 years previously. He had a history of daily alcohol intake, severe respiratory insufficiency and heart failure. On admission to the ICU, he was given a loading dose of dexmedetomidine of 6 μg/kg/h for 10 minutes, followed by an infusion at a rate of 0.2 to 0.7 μg/kg/h (titrated to the desired level of sedation) for 12 hours. Two hours after the start of the infusion, the patient exhibited hypotension (blood pressure of 70/40 mm Hg), but this resolved after crystalloid infusion without the need for vasopressor drugs. The patient recovered spontaneous ventilation 6 hours after surgery and was extubated at 6 hours and 15 minutes. The patient required no morphine or other analgesic during the 12-hour dexmedetomidine infusion. He did require morphine for pain after the infusion was terminated.

3. A 68-year-old male patient was admitted to the ICU after undergoing coronary artery bypass surgery for three-vessel disease. He had non-insulin-dependent diabetes mellitus and a history of atrial fibrillation and myocardial infarction. He was a nonsmoker who drank a glass of wine per day. Dexmedetomidine was administered at a loading dose of 6 μg/kg/h for 10 minutes followed by a maintenance dose of 0.2 to 0.3 μg/kg/h. The patient required no midazolam or morphine while receiving dexmedetomidine. His Ramsay Sedation Score was 6 during the first hour (baseline score, i.e., the patient was fully anaesthetized after surgery), then decreased to 4 and subsequently reached 3. A transient increase in blood pressure occured one hour into the postoperative course. The patient was extubated at approximately 6 hours, and his blood pressure increased again after the dexmedetomidine infusion was discontinued.

4. A 55-year-old male patient with a history of alcohol abuse underwent surgery for head and neck cancer. A dexmnedetomidine infusion (0.5 to 0.7 μg/kg/h) was started when the patient arrived in the ICU. He maintained hemodynamic stability throughout the infusion and exhibited no withdrawal symptoms. He required only 2 mg of morphine and 2 mg of midazolam immediately after extubation.

5. A 47-year-old male patient with a history of high alcohol intake underwent removal of a pharyngeal tumor and reconstruction with a jejunal flap. The surgical procedure lasted 10 hours during which the patient lost 3000 ml of blood and required transfusion of six units of blood. In the ICU, dexmedetomidine was administered in a loading dose of 6 μg/kg/h for 10 minutes followed by maintenance doses of 0.4 μg/kg/h for 35 minutes, 0.6 μg/kg/h for 20 minutes, and then 0.7 μg/kg/h for the remainder of the infusion. The patient remained calm and cooperative while receiving dexmedetomidine and his Ramsey Sedation Score was easily maintained between 2 and 3. He received a 2 mg dose of midazolam at 46 minutes and again at 66 minutes after the start of the dexmedetomidine infusion. Considering the nature of the surgery and the patient's history of alcohol consumption, initial postoperative morphine requirements were quite modest (24 mg). Yet, the morphine dose required escalated to 76 mg after the infusion of dexmedetomidine was discontinued.

6. A 35-year-old male patient with a history of "binge" drinking suffered bilateral lung contusions, several cracked ribs, and a large pelvic fracture in a traffic accident. He had uneventful general anesthesia during a 6-hour operation to repair his fractured pelvis. The blood loss was 400 ml, requiring a six-unit blood transfusion with cell saver. The patient received 70 mg of morphine intraoperatively. In the ICU, dexmedetomidine was administered at a loading dose of 6 μg/kg/h for 10 minutes.

The maintenance infusion was initiated at a rate of 0.4 μg/kg/h and was increased to 0.7 μg/kg/h during the first 3 hours. The patient's Ramsey Sedation Score was maintained at approximately 4. He was calm, comfortable, and required no morphine or midazolam. The patient was eligible for extubation at 6 hours. However, as this occured at 2:00 am, a decision was made to continue mechanical ventilation until the following morning. The dexmedetomidine dose varied between 0.3 and 0.5 μg/kg/h for approximately the final 160 minutes of the infusion.

The patient was awake, alert, and able to communicate in writing that he wanted the endotracheal tube removed. When the maximum allowable dose of dexinedetomidine, per protocol, was reached and when the patient became agitated and insistent over the removal of his endotracheal tube, doses of midazolam (totaling 16 mg) were administered. Despite his agitation, the patient remained free of pain and required no morphine while on dexmedetomidine. After extubation and cessation of the dexmedetomidine infusion, the patient required 4 mg of morphine before discharge from the ICU and nearly 50 mg of morphine during the first few hours after he returned to the ward. This need for more analgesia was considered a physiological response to pain, rather than a rebound effect.

7. A 60-year-old male alcoholic (35 units per week with fatty changes on liver ultrasound) underwent repair of an abdominal aortic aneurysm. He had a 40-year history of smoking, hypertension, angina pectoris, and pulmonary fibrosis. The surgery was technically difficult and took 3 hours. Blood loss was 3100 ml, and 6 units of blood were transfused. Morphine (30 mg) was administered intraoperatively. The patient was haemodynamically stable on arrival in the ICU. Dexmedetomidine was started at a loading dose of 6 μg/kg/h for 10 minutes followed by a maintenance dose of 0.4 μg/kg/h titrated to 0.7 μg/kg/h by the second hour. The Ramsey Sedation Score was maintained at approximately 4. Morphine requirements fluctuated markedly during the patient's first 6 hours in the ICU.

The patient was awake, oriented, and able to communicate that he was experiencing significant pain. At approximately 7 hours, with the dexmedetomidine dose at 0.5 μg/kg/h, it was determined that the entire graft was tearing off and the bottom disintegrating and pulling away from the posterior abdominal wall. Morphine requirements continued to escalate due to ongoing bleeding. The use of higher infusion rates of dexmedetomidine was limited by the presence of haemodynamic instability as a consequence of the bleeding. The patient was subsequently returned to surgery. Timely surgical intervention was facilitated by the patient's ability to communicate the breakthrough pain he experienced while receiving dexmedetomidine.

8. A patient underwent rectal extirpation and colostomy placement. Propofol was used for induction of anesthesia and oxygen/nitrous oxide/isoflurane for maintenance. In addition, remifentanil was started just after induction and continued until after the patient arrived in the ICU. A propofol infusion (70 mg) was also administered as the patient was transported to the ICU. By the

time the patient arrived in the ICU, he was awake but agitated and restless with a Ramsey Sedation Score of 1. Propofol and remifentanil were stopped within minutes of the patient's arrival. Repeated bolus doses of propofol 10 mg were required to manage the patient's agitation. A dexmedetomidine loading dose (0.4 μg/kg/h) was administered with propofol 20 mg at approximately 25 minutes after arrival in the ICU and was followed by infusions of dexmedetomidine 0.7 μg/kg/h and propofol 4 mg/kg/h. Repeated doses of morphine 2 mg were required during the first 20 minutes of dexmedetomidine infusion. The patient's Ramsey Sedation Score continually increased until the patient was oversedated with a score of 6. Approximately two hours after arrival in the ICU, the propofol infusion was reduced to 2 mg/kg/h and subsequently to 1 mg/kg/h. At 3 hours, propofol was discontinued and the dexmedetomidine infusion was tapered to 0.2 μg/kg/h. No additional propofol or morphine was required.

This case illustrates the importance of administrating dexmedetomidine before the analgesics administered pre-ICU have has lost their effect. This is particularly important when an agent with a very short half-life, such as remifentanil, is used. Experience with intraoperative remifentanil, in particular, has shown that due to its very rapid offset, postoperative pain is perceived early, thereby increasing the requirement for postoperative analgesia.

9. A 60-year-old man with renal carcinoma underwent an uncomplicated 3-hour radical nephrectomy. He had no significant previous medical history. During surgery, he received balanced anesthesia. Postoperatively, the patient was comfortable, experienced no respiratory difficulties, and was discharged from the ICU the following day. While receiving dexmedetomidine, he had a Ramsey Sedation Score of 3. He had no major gas exchange problems and $PaCO_2$ was stable during mechanical ventilation, assisted spontaneous breathing, extubation, and spontaneous breathing. His breathing pattern was essentially unchanged in the immediate postoperative period, while on assisted spontaneous breathing and after extubation. This patient's experience exemplifies the absence of a respiratory depressant effect with dexmedetomidine.

10. A 58-year-old female patient was scheduled for double coronary bypass surgery. Her past history revealed high blood pressure, angina pectoris, and type II diabetes. Intraoperatively, she received sufentanil, midazolam, pancuronium, and propofol. She arrived in the ICU at 7:20 pm and received a bolus of 1 μg/kg of dexmedetomidine over 10 minutes followed by an infusion of 0.4–0.7 μg/kg/h. Extubation took place at 7:50 am the next morning and dexmedetomidine was continued until 1:40 pm. She had an uneventful post-operative course. While on dexmedetomidine and intubated, she had a Ramsey Sedation Score of 4. She was calm, easily arousable, and well- oriented. She was not frightened by her surroundings (noises, personnel, and monitoring devices). After extubation, the dexmedetomidine infusion was progressively decreased to 0.3 μg/kg/h and her Ramsey Sedation Score oscillated between 2 and 3. She remained calm, cooperative and had no respiratory depression. She required no additional sedatives and very little analgesia during the dexmedetomidine infusion. After the dexmedetomidine infusion was stopped, she became restless, uncomfortable, and loquacious. Her anxiety profile differed considerably on and off medication. When questioned, she had no amnesia of her ICU stay, yet exhibited no distress or unpleasant recall.

11. A 54-year-old male patient underwent quadruple coronary bypass surgery. He had a 35-year history of excessive alcohol intake, but had reduced his consumption during the 6 weeks preceding surgery. Even though alcoholic patients commonly exhibit increased levels of anxiety and agitation in the ICU, this individual had an excellent postoperative course while receiving dexmedetomidine. He remained calm and quiet, yet well oriented. The dexmedetomidine infusion was maintained between 0.3 and 0.7 μ/kg/h and no additional sedatives were required. He was extubated the evening of his surgery, however, the dexmedetomidine infusion was continued until the next morning. On questioning, he indicated that he was extremely satisfied with his stay in the ICU.

12. A 49-year-old female patient underwent aortic valve replacement through a Ross procedure. The patient was unaware of her cardiac condition until the week preceding her surgery, was not psychologically prepared, and exhibited a high degree of anxiety preoperatively. On arrival in the ICU, she received a dexmedetomidine bolus of 1 μg/kg over a 10-minute period followed by a dexmedetomidine infusion between 0.2–0.5 μg/kg/h. She was extubated the evening of her surgery and dexmedetomidine was continued through until the next morning. During her postoperative course, the patient was calm, had no fear or apprehension, and was well oriented even though she had a little amnesia. She had excellent evolution and was very comfortable with her ICU experience.

13. The patient was a hypertensive, 51-year-old male with nephrolithiasis and a "silent" left kidney. He was admitted for a nephrectomy. Comorbidities included a hiatal hernia, gastric ulcer and diverticulum, and hepatic fatty metamorphosis. Other than these abnormalities, physical examination was within normal limits. His operative course and anaesthetic course were uneventful and he reached the ICU with a baseline Ramsey Sedation Score of 4. The desired level of sedation was very easily achieved with little dose adjustment of the infused dexmedetomidine as shown in FIG. 2. The patient could be easily roused and was able to communicate his needs to the nursing staff. Despite the presence of an endotracheal tube, he remained calm and asleep when free of external stimuli. The patient was extubated at 6 hours after ICU admission. Despite frequent assessments of his pain and opportunities to request additional analgesia, he required only a single dose (2 mg) of morphine sulfate at 6 hours into the study period. His postoperative course was uneventful except for one episode of moderate hypotension 14 hours after the initiation of dexmedetomidine administration and nearly 3 hours after the discontinuation of dexmedetomidine infusion. The patient responded to crystalloid infusion and the episode was attributed by the physician to the effects of morphine and possibly a mild volume deficit. Post-study, the patient's only complaint was somatic pain at the incision site. When interviewed, the patient stated that although the presence of the endotracheal tube was uncomfortable, were he to be readmitted to the unit he would request the same sedative he had received during the present hospitalization.

14. A 42-year-old male who had undergone coronary artery bypass surgery arrived in the ICU with a Ramsey

Sedation Score of 5 (asleep, sluggish responses to light glabellar tap or loud auditory stimuli). A loading dose of dexmedetomidine 6 μg/kg/h was administered followed by maintenance infusion at a dose of 0.4 μg/kg/h. The patient had a Ramsey Sedation Score of 6 (asleep, no response) for the first half hour. However, the infusion was rapidly and easily titrated to achieve and maintain a score of 2 (cooperative, oriented, tranquil) or a score of 3 (patient responds to commands) during the remainder of his stay in the ICU. No evidence of haemodynamic instability was observed and no opiate was required. The patient was extubated at approximately 6 hours and the rest of his ICU course was uneventful. He experienced moderate pain after extubation and the pain was easily controlled with a single injection of morphine 2 mg.

15. A 58-year-old male underwent valve replacement for aortic stenosis. In the ICU, he received a dexmedetomidine infusion titrated to achieve a Ramsey Sedation Score of approximately 3. He was oriented and cooperative. At one point, the infusion rate was increased because the patient began to experience pain. Importantly, he was able to communicate his need for pain relief, and dose titration rapidly restored his comfort rapidly.

16. The patient was a 62-year-old male, New York Heart Association class III with aortic regurgitation, left ventricular hypertrophy, and a dilated ascending aorta. He also had arterial hypertension and exertional angina (Canadian class II) with a normal coronary arteriogram. His preoperative medication was propranolol. The patient underwent normothermic cardiopulmonary bypass with replacement of the aortic valve and a Bentall procedure. He was weaned uneventfully from the pump after the 6-hour procedure and received no postoperative inotropic support. The course in the ICU was uneventful. The hemodynamic profile was smooth without hypotension or episodes of bradycardia. Although the patient did show an increase in blood pressure following discontinuation of dexmedetomidine, he entered the study with established hypertension.

The cases described above illustrate the benefits of dexmedetomidine sedation in critically ill patients. Appropriately sedated, the patients were oriented, physiologically stable and experiencing minimal pain, discomfort and anxiety. It is current practice to stop sedative drugs during ventilator weaning and after extubation to avoid respiratory depression. Such practice is not necessary with dexmedetomidine. Furthermore, dexmedetomidine increases patient compliance with therapeutic interventions (e.g., mobilization or chest physiotherapy) by removing fear of pain. This is a remarkable constellation of effects for a single medication.

Those skilled in the art will recognize that while specific embodiments have been illustrated and described, various modifications and changes may be made without departing from the spirit and scope of the invention.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A method of sedating a patient in an intensive care unit, which comprises administering to the patient an effective amount of dexmedetomidine of a pharmaceutically acceptable salt thereof, wherein the patient remains arousable and orientated.

2. The method according to claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt is the sole active agent.

3. A method of sedating a patient in an intensive care unit, comprising administering a pharmaceutical composition to the patient, wherein the pharmaceutical composition comprises an active agent and an inactive agent, wherein the active agent consists of dexmedetomidine or a pharmaceutically acceptable salt thereof, ane wherein the patient remains arousable and orientated.

4. The method according to claim 1, wherein the dexmedetomidine pharmaceutically acceptable salt thereof is administered in an amount to achieve a plasma concentration of 0.1–2 ng/ml.

5. The method according to claim 4, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is administered intravenously.

6. The method according to claim 5, wherein a loading dose and a maintenance dose of dexmedetomidine are administered.

7. The method according to claim 6, wherein the patient is a human.

8. The method according to claim 7, wherein the loading dose of dexmedetomidine is 0.2–2 μg/kg.

9. The method according to claim 8, wherein the loading dose is administered in about 10 minutes.

10. The method according to claim 7, wherein the maintenance dose of dexmedetomidine is 0.1–2.0 μg/kg/h.

11. The method according to claim 10, wherein the maintenance dose is 0.2–0.7 μg/kg/h.

12. The method according to claim 11, wherein the maintenance dose is 0.4–0.7 μg/kg/h.

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