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

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(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 GLAB TAP OR LOUD AUDITORY STIMULUS
5	ASLEEP, SLUGGISH RESPONSE TO LIGHT GLABELLAR TAP OR LOUD AUDITORY STIMULUS
6	ASLEEP, NO RESPONSE

FIG. 1

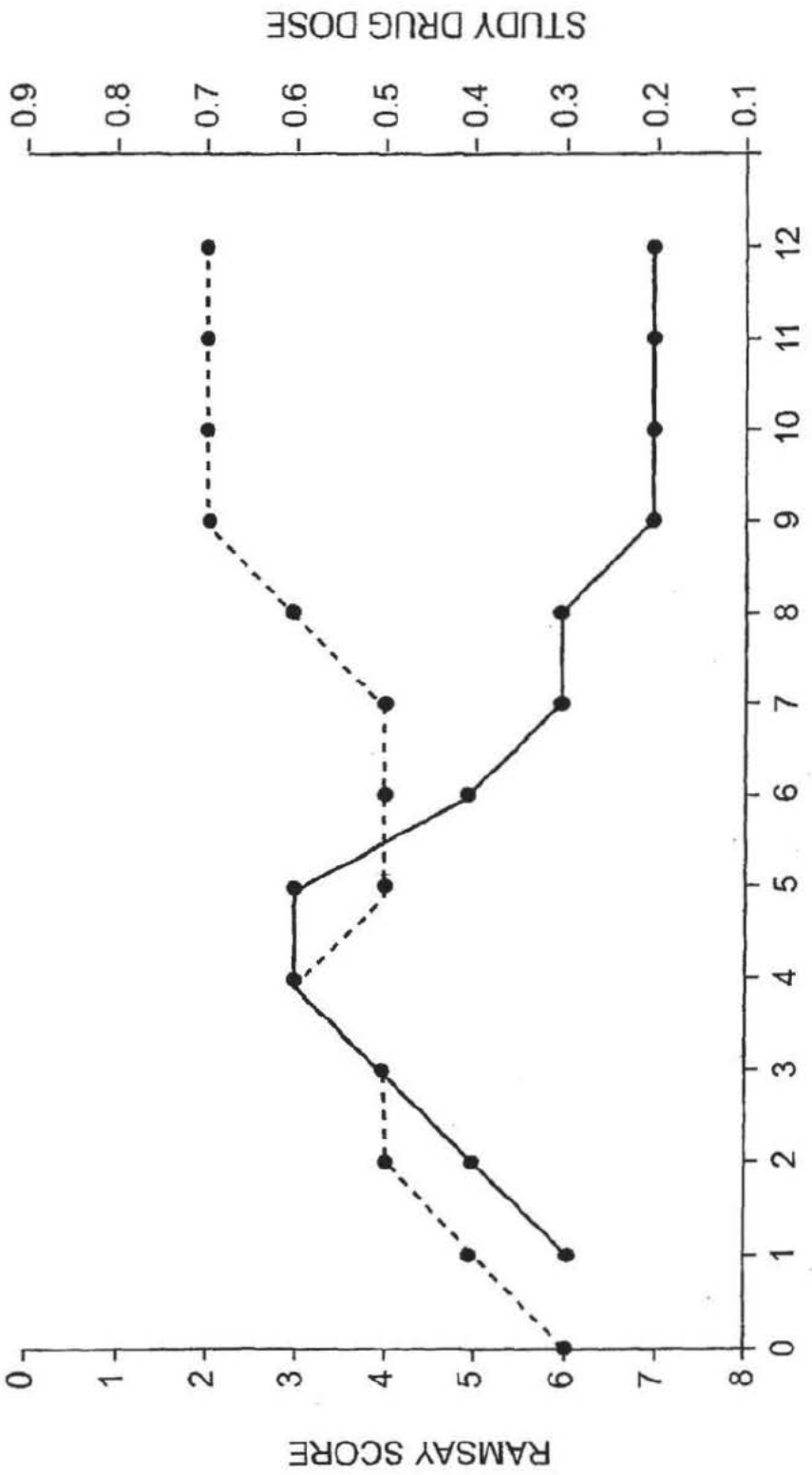


FIG. 2

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.

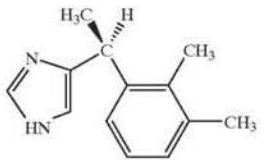
α_2-adrenoceptor agonists are being evaluated in general anaesthetic practice because of their sympatholytic, sedative, anaesthetic, and hemodynamic stabilizing effects. Tryba et al. discussed the usefulness of α_2-agonists in situations where patients with withdrawal symptoms are treated in the ICU (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 imnmunosuppression. 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

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