Trial decision

Invalidation No. 2015-800233

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The case of trial regarding the invalidation of Japanese Patent No. 4,606,581, entitled "USE OF DEXMEDETOMIDINE FOR ICU SEDATION" between the parties above has resulted in the following trial decision:

Conclusion

The trial of the case was groundless.

The costs in connection with the trial shall be borne by the demandant.

Reason

No. 1 History of the procedures

The application of Patent No. 4,606,581 (hereinafter referred to as “the patent

application") is derived from Japanese Patent Application with an international filing date of March 31, 1999 (claiming priority under the Paris Convention on April 1, 1998 and December 4, 1998 (US), both in the United States), and registered as a patent right on October 15, 2010.

In response, the Demandant demanded an invalidation trial for the invalidation of the Patent with a written demand for trial dated December 28, 2015.

The history of procedure in the Invalidation Trial of the case is as follows.

April 25, 2016	Written answer (Demandee)
August 19, 2016	Request for intervention (Intervenor: Nipro Corporation)
November 8, 2016	Decision to permit the intervention by the above Intervenor (Body)
December 1, 2016	Notification of matters to be examined (Body)
January 18, 2017	Written Statement (Intervenor)
January 24, 2017	Oral proceedings statement brief (Demandant)
February 7, 2017	Written statement (Demandee)
February 7, 2017	First Oral proceeding

No. 2 The patent invention

The inventions according to Claims 1 to 12 of the subject patent should be specified by the matters recited in Claims 1 to 12 of the Claims of the subject patent as follows (hereinafter referred to as "patent invention 1" to "patent invention 12" respectively, also collectively referred to as "the patent invention.")

"[Claim 1]

Use of dexmedetomidine or a pharmaceutically acceptable salt thereof in the manufacture

of a medicament for use in sedating a critically ill patient who is given intensive care, wherein the patient remains arousable and orientated.

[Claim 2]

The use according to claim 1, wherein the dexmedetomidine or a pharmaceutically acceptable salt thereof is the sole active agent or essentially the sole active agent.

[Claim 3]

The use according to claim 1 or 2, wherein the dexmedetomine or a pharmaceutically acceptable salt thereof is to be administered in an amount to achieve a plasma concentration of 1 to 2 ng/ml.

[Claim 4]

Use according to claim 3, wherein the dexmedetomidine or a pharmaceutically acceptable salt thereof is to be administered intravenously.

[Claim 5]

Use according to claim 4, wherein a loading dose and the maintenance dose of dexmedetomidine are to be administered.

[Claim 6]

Use according to claim 5, wherein the loading dose and the maintenance dose are to be administered to a human.

[Claim 7]

Use according to claim 6, wherein the loading dose of dexmedetomidine is 0.2 to 2 μg/kg.

[Claim 8]

Use according to claim 7, wherein the loading dose is to be administered in about 10 minutes.

[Claim 9]

Use according to claim 8, wherein the loading dose of dexmedetomidine is 1 μg/kg.

[Claim 10]

Use according to claim 6, wherein the maintenance dose of dexmedetomidine is 0.1 to 2.0 μg/kg/h.

[Claim 11]

Use according to claim 10, wherein the maintenance dose of dexmedetomidine is 0.2 to 0.7 μg/kg/h.

[Claim 12]

Use according to claim 11, wherein the maintenance dose of dexmedetomidine is 0.4 to 0.7 μg/kg/h."

No. 3 Argument by both parties and means of proof

1 Demandant's allegation of reasons for invalidation and means of proof submitted

According to the written demand and Oral proceedings statement brief submitted by Demandant, Demandant argues that the inventions recited in Claims 1 to 12 of the scope of claims of Patent No. 4,606,581 have the following reasons for invalidation 1 and 2, and submits the following documentary evidences as a means of proof.

[Reasons for invalidation 1]

The inventions 1 to 4 of the subject patent are identical to the inventions described in Evidence A No. 1. Thus these inventions are not patentable under the provision of Article 29(1)(iii) of the Patent Act. Consequently, the patents for these inventions

correspond to the inventions specified in Article 123(1)(ii) of the Patent Act and should be invalidated.

[Reasons for invalidation 2]

The inventions 1 to 12 were easily conceivable by a person skilled in the art on the basis of the inventions described in Evidence A No. 1 and Evidence A No. 2 in view of well-known technique, and thus could not be granted a patent under the provision of Article 29(2) of the Patent Act. Therefore, the patent corresponds to the provision of Article 123(1)(ii) of the Patent Act and should be invalidated.

[Means of proof]

Evidence A No. 1: Anesthesiology, Vol. 82, No. 3, 1995, pp. 620-633

Evidence A No. 2: Anesthesia & Analgesia, Vol. 75, No. 6, 1992, pp. 940-946

Evidence A No. 3: Pharmacology & Toxicology, 1991, Vol. 68, pp. 394-398

Evidence A No. 4: Anesthesiology, Vol. 77, 1992, pp. 1125-1133

Evidence A No. 5: Chest, Vol. 104, No. 2, 1993, pp. 566-577

Evidence A No. 6: Critical Care Nursing Quarterly, Vol. 15(2), 1992, pp. 52-74

Evidence A No. 7: MEDICAL VIEW CO., LTD., Stedman's Medical Dictionary 2nd Edition, page 719, published on March 10, 1989

<All the above are attached to the written demand for trial>

Evidence A No. 8: http://www.pmda.go.jp/drugs/2004/P200400001/index.html

"Efficacy and effects (draft), dose regimen and dosage amount, precautions (draft) and the ground of the design"

Evidence A No. 9: The Journal of Thoracic and Cardiovascular Surgery, Vol. 110, Number 5, pp. 1461-1469, November 1995

Evidence A No. 10: Anesthesiology, Vol. 84, No. 6, pp. 1350-1360, June 1996

Evidence A No. 11: http://www.barttersite.org/mag_children_heart_surgery.htm American Heart Journal, Vol. 139, No. 3, March 2000

Evidence A No. 12: J Crit Care, 2015 Dex; 30(6): 1238-1242

Evidence A No. 13: Pharmaceutical and Food Safety Bureau, Evaluation and Licensing Division, Examination report (2), pages 1 to 57, October 22, 2003

Evidence A No. 14: Intensive Care Medicine, (1990)16: pp. 265-266

Evidence A No. 15: Anesth Analg, 1997; 85, pp. 1136-1142

Evidence A No. 16: American Society Anesthesiologists, 2012 Operating Room Design Manual, Chapter 14, pp. 57-72

Evidence A No. 17: Journal of Perioperative and Critical Intensive Care Nursing, Vol. 2, Issue 3, 2016, Open Access Journal

<All the above are attached to the Oral proceedings statement brief filed on January 24, 2017>

2 Demandee's argument and means of proof submitted

According to the written reply and written statement submitted by Defendant, Defendant argues that the Patent does not have the above reasons for invalidation 1 and 2 and submits the following documentary evidences as means of proof.

[Means of proof]

Evidence B No. 1: Written opinion submitted on May 17, 2010 in the prosecution process of the Patent

Evidence B No. 2: Marquette Series 8500 Holter monitor explanatory booklet and its translation

Evidence B No. 3: Takayuki Imai "Definition of intensive care medicine" Journal of Japanese society of intensive care medicine, 2009, Vol. 16, page 503

Evidence B No. 4: Translation of Evidence A No. 1

Evidence B No. 5: Translation of Evidence A No. 6

No. 4 Description of Evidences

Demandant pointed out that Evidence A No. 1 to No. 17 have the following descriptions.

(1) Evidence A No. 1

"Effects of Perioperative Dexmedetomidine Infusion in Patients Undergoing Vascular Surgery" (title)

"Background: Dexmedetomidine is a highly selective alpha2-adrenergic agonist, and in healthy patients improves preoperative, perioperative, or postoperative (perioperative) hemodynamic stability, whereas it lowers blood pressure and heart rate. The purpose of the test was to preliminarily evaluate the hemodynamic action of Dexmedetomidine to be administered preoperatively, perioperatively, or postoperatively in patients at high risk for coronary arteriopathy.

Method: To twenty-four patients undergoing vascular surgery were continuously infused with placebo or one unit of three dosages of Dexmedetomidine; i.e., targeted

plasma concentrations of 0.15 ng/ml (low dose), 0.30 ng/ml (medium-dose), or 0.45 ng/ml (high-dose) from 1 h before induction of anesthesia throughout the intraoperative period and for 48 h postoperatively. All the patients were subjected to a standard anesthesia, and hemodynamics were monitored. Blood pressure, heart rate and Holter electrocardiogram were monitored, and further the monitoring of preoperative continuous 12-Lead ECG, perioperative anesthetic level and regional wall motion (ECG), and postoperative cardiac enzyme were added.

Result: Preoperatively, in dexmedetomidine dose patients, lowering of heart rate (low-dose 11%, medium-dose 5%, high-dose 20%) and lowering of systolic blood pressure (low-dose 3%, medium-dose 12%, high-dose 20%) were observed. Intraoperatively, a greater amount of vascular agonist was required in the dexmedetomidine dose group to maintain hemodynamics within a certain range. Postoperatively, the dexmedetomidine groups had significantly less tachycardia than the placebo group (minutes/monitored hours) (placebo 23 minutes/hr; low-dose 9 minutes/hr, P = 0.006; medium-dose 0.5 minutes/hr, P = 0.004; high-dose 2.3 minutes, P = 0.004). In any group, bradycardia was rarely observed. No myocardial infarction identifiable trend in clinical test result was observed.

Conclusion: The infusion of dexmedetomidine up to the targeting plasma concentration of 0.45 ng/ml appeared to be beneficial in perioperative hemodynamic management of patients undergoing vascular surgery but required greater intraoperative pharmacologic intervention to support blood pressure and heart rate.

(Key words: Dexmedetomidine: hemodynamics. Dose-effect. Heart: coronary artery disease. Sympathetic nervous system, alpha2-adrenergic agonist: dexmedetomidine)" (page 620, Abstract)

"Anesthetic Management

The night before surgery, patients received 2 mg lorazepam orally. In the operating room, study drug infusion was started 1 h before induction of anesthesia. Patients then

breathed oxygen while anesthesia was induced with alfentanil (up to 30 micro gram/kg) and thiopental (up to 3 mg/kg). Vecuronium (0.1 mg/kg) was administered to achieve muscle relaxation before tracheal intubation and as needed thereafter."

(page 621, the right column, lines 29 to 37)

"Surgical and postoperative stress evoke an endocrine response that manifests as stimulation of the hypothalamus-pituitary-adrenal axis, renin-angiotensin axis, and the sympathetic nervous system. Stimulation of the sympathetic nervous system increases the levels of circulating plasma norepinephrine and epinephrine, increasing blood pressure and heart rate and the incidence of postoperative complications. The hyperdynamic changes predispose the myocardium to ischemia, especially in the patient population with decreased reserve for coronary blood flow. Preoperative, perioperative, and postoperative ischemia are associated with a significant increase in postoperative morbidity and mortality. Attenuating the perioperative stress response could decrease the incidence of myocardial ischemia and thereby reduce the incidence of perioperative morbidity and mortality in patients at high risk for myocardial ischemia.

Several clinical studies suggest that alpha2-adrenergic agonists might be effective in blunting the perioperative stress response and that clonidine may have perioperative antiischemic effects. Dexmedetomidine is an alpha2-adrenergic agonist with a 10-fold greater alpha2/alpha1-receptor selectivity than clonidine. In healthy volunteers, dexmedetomidine decreases circulating catecholamines by up to 90% and, like clonidine, has antinociceptive and sedative effects. In healthy surgical patients, dexmedetomidine increases hemodynamic stability, decreases anesthetic requirements, and blunts the hyperdynamic response to intubation. The sympatholysis also results in potentially adverse clinical effects, such as a decrease in blood pressure and bradycardia. Such hemodynamic changes might not be tolerated by patients with vascular disease or severe myocardial disease.

Thus far, dexmedetomidine has been administered only to healthy volunteers and

healthy surgical patients. Therefore, to perform a preliminary evaluation of the feasibility and effects of perioperative administration of dexmedetomidine in high-risk surgical patients, we studied three consecutively increasing doses of an infusion of dexmedetomidine in vascular surgery patients, a population with a high incidence of coronary artery disease (CAD) who might benefit significantly from increased perioperative hemodynamic stability.

Methods

Patients

With approval from our Human Research Committee and written informed consent, we studied 25 patients with or at high risk for CAD who were scheduled for vascular surgery at the San Francisco Veterans Affairs Medical Center. Study entry criteria included one or more of the following: a history of classic angina pectoris; a history of myocardial infarction; electrocardiographic (ECG) evidence of Q waves typical of infarction without a history; CAD detected by angiography; or the presence of two or more risk factors for CAD, including cigarette smoking, treatment for hypertension, treated diabetes mellitus, or hypercholesterolemia (> 240 mg/dL). Excluded from study were patients with unstable angina, uninterpretable preoperative ECGs (left bundle branch block), patients taking clonidine or tricyclic antidepressants, and those who did not receive the study drug continuously for at least the first 24 postoperative hours. Cardiac medications were continued until the night of surgery.

Experimental Protocol

The study was a double-blind, randomized, dose-escalation trial using three different doses of dexmedetomidine and placebo. Twenty-four patients were divided into

three groups of eight to form low-, medium-, and high-dose test groups, each having six patients who received dexmedetomidine and two who received placebo. Thus, six patients received placebo during the study. The number of patients used in this study was not based on power calculations. Study began with the low-dose group, and once this dose was determined to be tolerable, proceeded to the medium-dose group, then, after the same determination, the high-dose group. Initially, 25 patients were enrolled in the study, but one (from the high-dose group) was excluded when dexmedetomidine was discontinued within 24 h of administration to permit an emergent return to surgery.

Dexmedetomidine was administered by a computer-controlled infusion pump (CCIP) targeting plasma concentrations of 0.15 ng/ml (low-dose), 0.30 ng/ml (medium-dose), and 0.45 ng/ml (high-dose). STAN-PUMP software (Steve Shafer, Stanford University, Palo Alto, CA) was used to run the infusion pump (Harvard Apparatus 22, Harvard Apparatus, South Natick, MA). The STANPUMP software updated the infusion rate at 10-s intervals using dexmedetomidine pharmacokinetic data to allow drug delivery to targeted plasma concentrations. The infusion rate data were stored in a laptop computer, which was used to run the STANPUMP program. To study the effect of dexmedetomidine in awake and anesthetized patients, infusion was begun 1 h before induction of anesthesia and continued throughout the intraoperative period and for 48 h postoperatively. The average amount of dexmedetomidine infused was 2.64 micro gram/kg (range 2.30-3.75 micro gram/kg), 5.31 micro gram/kg (range 4.40-5.97 micro gram/kg), and 8.03 micro gram/kg (range 5.57-9.87 micro gram/kg) for the low-, medium-, and high-dose groups, respectively. Patients were not permitted to ambulate during study drug infusion." (page 620, right column, line 12 to page 621, right column, line 28)

"Postoperative Analgesia

Postoperative analgesia was provided by intravenous morphine sulfate, delivered by a patient-controlled analgesia (PCA) pump. The initial PCA setting was a 1-mg bolus dose with a lock-out interval of 6 min. For inadequate analgesia, additional 2-mg doses of

morphine were administered intravenously as needed. If analgesia remained inadequate after the additional 2-mg bolus doses, the PCA dose was increased in increments of 0.5 mg.

Analgesia was assessed using a visual analog scale (VAS), comprising a 100-mm horizontal line with one pole representing 'no pain' and the other 'worst pain imaginable.' The scale was administered every 4 h postoperatively for the first 48 h, as long as the patient was awake. Patients assessed their pain at rest and rated the severity of the worst pain since the last assessment." (page 623, right column, line 5 from the bottom to page 624, left column, line 12)

"Sedation and Analgesia

After the 1-h infusion preceding induction of anesthesia, all patients in the medium- and high-dose groups fell asleep but were easily arousable. During the second postoperative day, there was no clinically observable sedation from the study drug. Postoperative VAS pain scores were similar among groups, and postoperative morphine requirements did not differ." (page 627, the right column, lines 25 to 32)

"The current study evaluated, in a preliminary manner, the effects of dexmedetomidine in high-risk patients undergoing vascular surgery. This study also is the first to administer dexmedetomidine as a continuous perioperative infusion over a 2-day period to cover the duration of most perioperative stress and hemodynamic lability. Our results suggest that a perioperative dexmedetomidine infusion to a targeted plasma concentration of 0.45 ng/ml can be used in high-risk vascular surgical patients if other drugs are given to offset the depression of heart rate and blood pressure." (page 628, left column, lines 8 to 19)

"Anesthetic Requirements and Sedation

Aho et al. reported that a continuous intraoperative dexmedetomidine infusion can

decrease the requirements for isoflurane by up to 90% in healthy patients. Our intraoperative use of alfentanil and nitrous oxide provided sufficient anesthesia for our vascular surgery patients, such that isoflurane requirements were low in all groups. Therefore, we cannot evaluate the potential reductive effect of dexmedetomidine on anesthetic requirements in vascular surgery patients. A study with minimal background anesthesia will be required to achieve this.

Several studies have reported dose-dependent sedative effects with dexmedetomidine. During the 1-h dexmedetomidine infusion preceding induction of anesthesia, the patients in our medium- and high-dose groups fell asleep but were easily arousable. Although the dexmedetomidine infusion had a sedative effect before induction, sedation was not observable the day after surgery. This is consistent with recent findings of tachyphylaxis to the anesthetic effects of dexmedetomidine in rats." (page 630, right column, line 6 from the bottom to page 631, left column, line 16).

"Conclusion

The hemodynamic effects of dexmedetomidine in vascular surgery patients appear to be similar to those in healthy volunteers. A dose of 0.45 ng/ml appeared to be most effective in blunting hemodynamic responses to perioperative stress but required greater intraoperative pharmacologic intervention to support blood pressure and heart rate. Further studies in a larger number of high-risk patients will be conducted to verify these preliminary results." (page 632, left column, lines 22 to 31)

(2) Evidence A No. 2

"Dexmedetomidine Infusion for Maintenance of Anesthesia in Patients Undergoing Abdominal Hysterectomy" (Title)

"The usefulness of intravenous dexmedetomidine infusion for maintenance of anesthesia was studied in patients anesthetized with thiopental, fentanyl, nitrous oxide, and oxygen. Isoflurane was added as needed. The study was conducted in two parts, the first of which was an open dose-response study that comprised 14 women undergoing abdominal hysterectomy. After a suitable infusion regimen of dexmedetomidine was determined according to hemodynamic criteria, 20 patients were included in a double-blind, randomized placebo-controlled trial (10 receiving dexmedetomidine, 10 saline solution). Dexmedetomidine was administered as a two-step infusion to rapidly achieve a steady-state plasma concentration. The infusion was started with an initial dose given over 10 min before the induction of anesthesia; at induction the maintenance rate was begun, which was continued until closure of the abdominal fascia. The infusion regimens of dexmedetomidine tested in the dose-response study ranged from 120 ng-kg^{-1}.min^{-1} followed by 6 ng-kg^{-1}.min^{-1}, to 270 + 13.5 ng-kg^{-1}.min^{-1}. In the second part of the study, an initial infusion of 170 ng-kg^{-1}.min^{-1} was chosen, followed by 10 ng-kg^{-1}.min^{-1} for maintenance. Anesthesia was induced with thiopental (4.0 mg/kg) and maintained with isoflurane in 70% nitrous oxide and oxygen. Isoflurane was administered according to predetermined hemodynamic criteria. Dexmedetomidine infusion did not completely abolish the need for isoflurane but diminished its requirement by >90% (P = 0.02). The heart rate response to endotracheal intubation was significantly blunted." (page 940, Abstract)

"The α_2-adrenergic agonists produce sedation and reduce anesthetic requirements in several animal models. The prototype of α_2-adrenergic agonist, clonidine, has been used for hemodynamic stabilizing effect and for its anesthetic-sparing effect during cardiopulmonary bypass, during vascular surgery, and in elderly patients. Postoperative clonidine infusion reduces heart rate and plasma norepinephrine, epinephrine, and vasopressin concentrations.

Dexmedetomidine, an imidazole derivative, is a selective and full α_2-adrenoceptor agonist possessing sedative properties. It is well tolerated but causes a dose-dependent decrease in arterial blood pressure and heart rate (HR) associated with a decrease in plasma

norepinephrine concentrations.

Sleepiness appears within 5 min after intravenous administration of dexmedetomidine and reaches its maximum within 15 min. A single intravenous bolus dose of dexmedetomidine administered 15 min before induction of anesthesia diminished thiopental requirement during cervical dilatation and uterine curettage procedures. Dexmedetomidine administered by a single intravenous injection attenuates hemodynamic responses to laryngoscopy and endotracheal intubation and decreases isoflurane requirement for anesthetic maintenance by 30%.

In this study, we evaluated the effects of a continuous, two-step intravenous infusion of dexmedetomidine on hemodynamic responses to laryngoscopy and endotracheal intubation and its usefulness during maintenance of anesthesia in patients undergoing abdominal hysterectomy." (page 940, left column, line 1 to right column, line 16)

"The first was an open dose-response study and comprised 14 women undergoing elective abdominal hysterectomy. The second part, accomplished after the suitable infusion regimen of dexmedetomidine had been determined, consisted of a double-blind, randomized, placebo-controlled trial involving 20 patients. All were healthy, normotensive, ASA physical status I or II women." (page 941, left column, lines 1 to 8)

"The first part of the study was an open dose-response trial. Dexmedetomidine, diluted in normal saline solution to a concentration of 10 μg/mL, was administered by a continuous, two-step infusion. Infusion rates had been calculated according to the methods previously described by Wagner and were based on pharmacokinetic variables reported by the manufacturer (elimination half-life 2.3 h; plasma clearance 12 mL-kg^{-1}-min^{-1}). The first regimen tested consisted of a 120-ng-kg^{-1}-min^{-1} loading infusion, administered over 10 min, followed by a 6-ng-kg^{-1}min^{-1} maintenance infusion, which was predicted to result in a 0.5-ng/mL steady-state plasma concentration of dexmedetomidine. In subsequent groups of patients, the initial rates was 170, 220, and 270 ng-kg^{-1}-min^{-1}, respectively. The corresponding maintenance rates were 8.5, 11, and 13.5 ng-kg^{-1}min^{-1}, respectively. The predicted steady-state plasma concentrations of dexmedetomidine were 0.7, 0.9, and 1.1

ng/mL." (page 941, the right column, lines 6 to 25)

"In the second part of the study, sedation was assessed upon arrival in the operating room and at 5 min after the beginning of the study drug infusion. Sedation was scored as 1= awake, eyes open; 2=asleep, easy to arouse.

The time to awakening, as determined by the time interval between the termination of nitrous oxide administration and eye-opening on request, was assessed." (page 942, left column, lines 5 to 13)

"Dose-Response Study

Four different infusion regimens (initial + maintenance rates) of dexmedetomidine were studied: 120 + 6 ng-kg^{-1}min^{-1} (n=3); 170 + 8.5 ng-kg^{-1}-min^{-1} (n=6); 220 + 11 ng-kg^{-1}-min^{-1}(n=3); 270 + 13.5 ng-kg^{-1}-min^{-1} (n=2). The four groups of patients were comparable with regard to age, weight, duration of operation, and the amount of perioperative fluid received." (page 942, the right column, lines 6 to 14)

(3) Evidence A No. 3

"Assessment of the Sedative Effects of Dexmedetomidine, an α2-Adrenoceptor Agonist, with Analysis of Saccadic Eye Movements" (Title)

"Abstract: Single intravenous doses (0.5 μg/kg and 1.0 μg/kg) of dexmedetomidine (4(5)-(1-(2,3-dimethylphenyl)ethyl)imidazole), a selective α2-adrenoceptor agonist, and saline placebo were administered to six healthy volunteers (4 males and 2 females) in a double-blind, placebo-controlled cross-over study. The effects on vigilance were assessed using both subjective estimation (visual analogue scale, VAS) and objective tests (critical flicker fusion frequency, CFF; the Maddox wing; saccadic eye movement analysis). Dose-dependent subjective sedation was seen in VAS measurements, and impairment of vigilance was observed in CFF, Maddox wing, and peak saccadic velocity, while saccade

latency was not influenced by dexmedetomidine. The changes in vigilance were concurrent with moderate reductions in blood pressure and heart rate. CFF, the Maddox wing and peak saccadic velocity all proved sensitive in the assessment of sedation induced by dexmedetomidine." (page 394, Abstract)

"Dexmedetomidine (4(5)-(1-(2,3-dimethylphenyl)ethyl)imidazole, fig. 1) is the pharmacologically active d-isomer of medetomidine, a specific and selective α2-adrenoceptor agonist. Medetomidine, a racemic mixture (1:1) of d- and l-enantiomers, is a highly lipophilic compound (Savola et al. 1986) with high affinity for α2-adrenoceptors (Virtanen *et al*. 1988). It is devoid of binding to or effects at μ- and δ-type opioid, dopamine D1 and D2, histamine H1, muscarinic, β-adrenergic, and benzodiazepine receptors (Virtanen *et al*. 1988). Medetomidine has a significantly higher α_2/α_1-selectivity ratio in receptor binding experiments than clonidine, the prototype of α_2-adrenoceptor agonists, (1620 versus 220 in rat brain cortical membranes; Virtanen *et al*. 1988) and compared with the latter drug, it is more effective as an α_2 agonist (Savola *et al*. 1986; Virtanen *et al*. 1988).

Dexmedetomidine, like other α_2-adrenoceptor agonists, exerts sympatholytic effects by activating inhibitory α_2-adrenergic receptors both in the central nervous system and on peripheral sympathetic nerve endings (Presynaptic autoreceptors) (Savola *et al*. 1986; MacDonald *et al*. 1988), which leads to inhibition of the release of noradrenaline (Langer 1981; Szemeredi *et al*. 1988). Reduction in sympathetic nervous activity is manifested as a dose-dependent decline in the plasma levels of noradrenaline (Scheinin *et al*. 1987; Kallio *et al*. 1989). In previous human volunteer studies, the pharmacodynamic effects of medetomidine have included dose-related reductions in blood pressure, heart rate, and cardiac output (Scheinin *et al*. 1987; Kallio *et al*. 1989&1990). Its most prominent subjective effects are sedation and decreased salivation (Scheinin *et al*. 1987). In animal experiments, medetomidine and dexmedetomidine have shown little or no effects on respiration (Bloor *et al*. 1989; Furst & Weinger 1990).

Apart from its wide use as an antihypertensive, clonidine, as well as some other α_2-adrenoceptor agonists, have been successfully used in connection with opioid (Gold *et al*. 1980) and alcohol withdrawal syndromes (Wilkins *et al*. 1983) as well as to abate cigarette craving after cessation of heavy smoking (Glassman *et al*. 1988). Due to their sedative and other sympatholytic effects, there has been increasing interest in α_2-adrenoceptor agonists and their usefulness in connection with anaesthesia (Longnecker 1987; Bloor 1988). In fact, and intravenous bolos dose of dexmedetomidine causes sedation and reduces the induction dose of thiopentone by 30% when used as premedication before anaesthesia and minor surgery, without having marked haemodynamic effects (Aantaa *et al*. 1990a&b). Dexmedetomidine may even be a complete anaesthetic by itself in sufficiently high doses in certain animal models (Segal *et al*. 1988; Doze *et al*. 1989).

The present study was conducted in order to objectively and quantitatively assess the sedative effects of single intravenous doses of dexmedetomidine in human volunteers." (page 394, left column, line 1 to right column, line 18)

"Six healthy volunteers participated after written informed consent (2 females and 4 males age 23.8±1.5 (mean±S.D.) years, height 175.3±14.8 cm, weight 67.3±15.7 kg). All were non-smokers. The health of the subjects was ascertained by detailed medical history, physical examination, and electrocardiogram. None of the volunteers had received any medications for a period of at least 2 weeks preceding the study. Alcoholic beverages were prohibited for 36 hr prior to each session, and caffeinated drinks and chocolate were not allowed from 10 p.m. on the preceding night. The subjects were advised to have a light standard breakfast and lunch on the day of the experiments. The protocol of the study was approved by the Ethics Committee of Turku University Hospital and the Finnish National Board of Health.

All experiments were carried out at the same time of day (1 p.m.-3 p.m.) in order to exclude diurnal variation from session to session. The intravenous test doses of 0.5 and 1.0 μg/kg of dexmedetomidine and an equal volume of saline were given using a double-blind

technique with balanced randomization. Consecutive sessions were at least one week apart for each subject. Upon arrival, an intravenous forearm cannula was inserted and continuous monitoring of the electrocardiogram and heat rate (HR) were started. Noninvasive measurements of systolic (BPS) and diastolic (BPD) blood pressure with an automated oscillometric device (Nippon Colin 203Y, Tokyo, Japan) as well as the subjective and objective assessments of sedation were recorded before and 5, 15, 30, 45, 60, 90 and 120 min. after the drug injection. The drug was injected slowly over 60 sec. after at least a 30 min. stabilizing period in the supine position. The experiments took place in a quiet dimly lit room." (page 395, left column, lines 8 to 34)

"Other subjective treatment-related effects were assessed by repeating a standard questionnaire and a VAS for dryness of mouth at the times mentioned above, and by urging the subjects to report all possibly drug-related symptoms and signs to the investigator." (page 395, left column, lines 49 to 53)

"Dose-dependent sedative effects were observed both by subjective and objective assessments (fig. 2). Drug-related subjective sleepiness appeared in 5 min. ($P<0.01$ after both doses), was maximal 15 min. after the drug injection, and lasted until the end of the session after both doses of dexmedetomidine ($P<0.05$ after the smaller dose and $P<0.01$ after the higher dose). Four of the six volunteers fell asleep several times from 5 min. until 1 hr after the injection of the highest dose of dexmedetomidine, but all remained easily arousable and the tests could be uninterruptedly performed. The smaller dose, although clearly sedative, did not cause as extensive tiredness. The VAS scores were significantly different between placebo and the smaller dose and between the smaller and the higher dose of dexmedetomidine ($F=10.54$, $P<0.001F=4.95$, $P<0.001$; and $F=4.95$, $P<0.001$, respectively)." (page 395, the right column, lines 8 to 22)

"

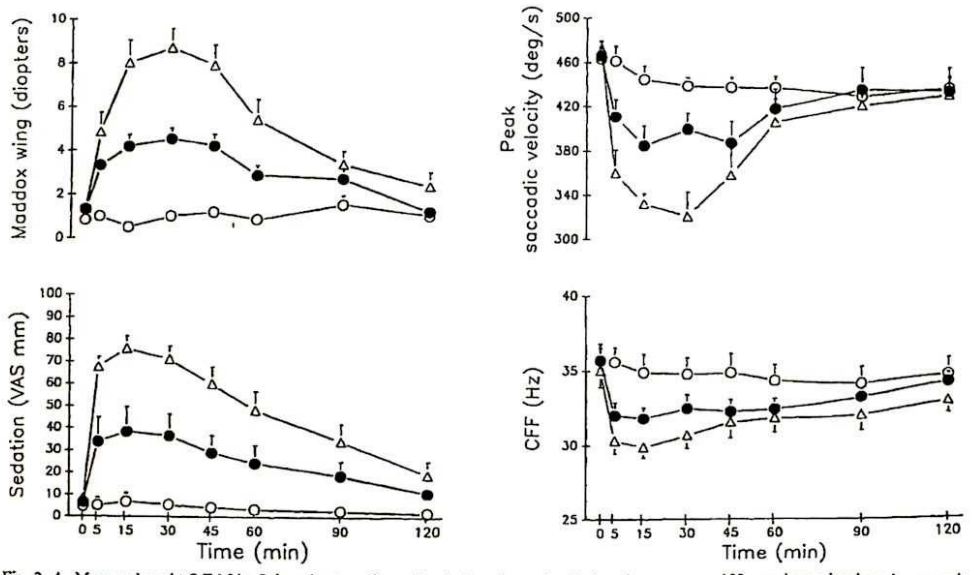

Fig. 2. A. Mean values (±S.E.M.) of six volunteers for subjectively estimated sedation, (as mm on a 100 mm long visual analogue scale (VAS): 0=fully alert; 100=almost asleep) and the Maddox wing scores (in diopters) after single intravenous doses of dexmedetomidine. B. Mean values (±S.E.M.) of critical flicker fusion frequency (CFF; in Hz) and peak saccadic velocity (degrees/s) after dexmedetomidine. Symbols: saline placebo (o), dexmedetomidine 0.5 μg/kg (●), 1.0 μg/kg (△).

" (page 396, Fig. 2)

(4) Evidence A No. 4

"Effects of Intravenous Dexmedetomidine in Humans: I. Sedation, Ventilation, and Metabolic Rate" (Title)

"Dexmedetomdine (DMED) is a highly selective centrally acting alpha2-adrenergic agonist thought to provide significant sedation without appreciable ventilatory effects. This double-blind, placebo-controlled experiment evaluated four dose levels of DMED (0.25, 0.5, 1.0, and 2.0 μg/kg intravenously over 2 min) in 37 healthy male volunteers. Measurements of sedation, arterial blood gases, resting ventilation, hypercapnic ventilatory response (HVR), and metabolic rate (O2 consumption and CO2 production) were

performed at baseline, 10 min after DMED infusion, and thereafter at the end of each subsequent 45-min period. DMED caused sedation resulting in loss of responsiveness in most of the subjects administered 1.0 and 2.0 μg/kg; sedation was evident for 195 min following 2.0 μg/kg ($P < .05$). Ten minutes following infusion of 1.0 and 2.0 μg/kg, Pa_{CO2} had increased by 5.0 and 4.2 mmHg, respectively ($P < .05$), and 60 min following 2.0 μg/kg, Tidal volume had decreased by 28% ($P < .05$). The placebo group showed a progressive increase in the HVR slope (50% increase by 330 min following the infusion; $P < .05$). Overall, across all the DMED doses, the slope was decreased ($P < .05$) at all times after DMED. The calculated ventilation at a Pa_{CO2} 55 mmHg was decreased (39%; $P < .05$) 10 min following 1.0 and 2.0 μg/kg, returning to control values by 285 min following 2.0 μg/kg. O_2 consumption decreased 16% ($P < .05$) at 10 min following 2.0 μg/kg; CO_2 production decreased (22% at 60 min). By 5 h postinfusion, both had returned to normal. Intravenous DMED caused sedation and sleep with minor decreases in resting ventilation, whereas the HVR was reduced slightly. The increase in oxygen consumption seen immediately after administration of DMED is not readily explained by the known physiologic effects of alpha$_2$-adrenergic agonists. (Key words: Metabolism: glucose, Sympathetic nervous system, alpha2-adrenergic agonist; dexmedetomidine. Ventilation: hypercapnic ventilatory response)" (page 1125, Abstract)

"Subjects

This double-blind, placebo-controlled study was approved by the UCLA Human Subject Protection Committee and all subjects gave written informed consent. Thirty-seven normal, healthy male volunteers between the ages of 18 and 45 years, weighing less than 100 kg, participated in this study. Each subject was free of significant cardiac or respiratory disease and had normal serum chemistry, liver function tests, CBC, urinalysis, and ECG prior to the study. If there was any evidence of acute or chronic disease, drug use, or routine use of medications, the volunteer was excluded from the study.

Dexmedetomidine was administered intravenously at four dose levels. All the

subjects in a given dose group were studied before proceeding to the next higher dose. Placebo-treated subjects were randomly interspersed within each dose group. In each of the 0.25, 0.5, and 1.0 μg/kg dose groups, 6 subjects received DMED and 2 received placebo. In the 2.0 μg/kg dose group, 10 subjects received DMED and 3 received placebo. Thus, a total of 37 subjects were studied, of which 9 received placebo. Each subject participated in only one experiment." (page 1125, right column, line 7 from the bottom to page 1126, left column, line 15)

"Measurements

Two baseline measurements were taken at 90 and 45 min prior to the infusion of the drug or placebo. The baseline values reported for all measurements are the averages of these two measurements. The test drug was infused by syringe pump (Harvard Apparatus, Billerica, MA) over 2 min. Ten minutes after the beginning of infusion, the first set of post-treatment measurements were made and these were repeated at 60- and 45-min intervals thereafter. At each period sedation, ventilation, arterial blood gases, oxygen consumption, and carbon dioxide production were measured as described below." (page 1126, left column, lines 15 to 4 from the bottom)

"Sedation / Anxiety

Subjects used a visual analog scale (VAS) to rate their states of sedation (1 = fully alert and 10 = asleep) and anxiety (0 = no anxiety and 10 = most severe anxiety imaginable). If, at the time the VAS scores were to be recorded, the subject was asleep and could not be awakened by voice command, a score of 100 was recorded for sedation and a score of zero was recorded for anxiety." (page 1126, left column, lines 3 from the bottom to right column, line 5)

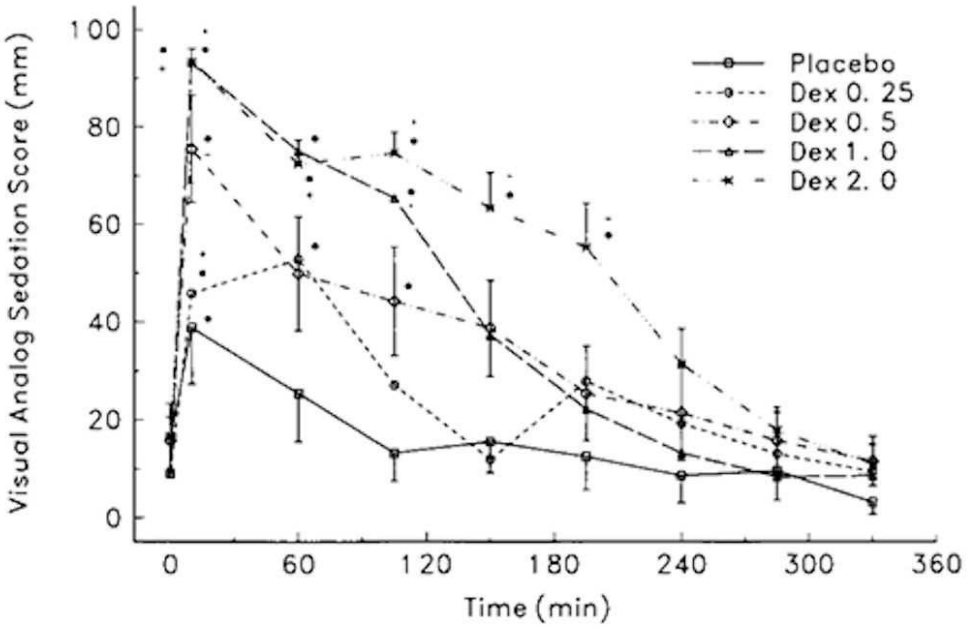

FIG. 1. Average sedation VAS for the four dose groups and placebo. For clarity SEM is shown for the placebo and 0.5 and 1.0 μg/kg groups. Time 0 is the average of the two pre-infusion baseline measurements. The first postdrug measurements were made at 10 min after the drug infusion. $^{*}P < .05$ different from the baseline (time = 0) measurement within a dose group. $^{+}P < .05$ different from the placebo group measurement at the same time point. "

" (page 1127, FIG.1.)

"By 4 h after infusion, all subjects were fully awake and alert, ambulatory, and able to be discharged home.

Sedation, as measured by a visual analog scale, showed a significant dose-related increase which peaked 10 min following DMED administration and declined over the remainder of the observation period. In the 1.0 (67%) and 2.0 (70%) μg/kg dose groups, most subjects fell asleep (unarousable by normal volume voice command). Sedation remained significantly increased for up to 195 min after DMED in the 2.0 μg/kg group. Anxiety scores were low during baseline measurements in all groups and did not change (increase or decrease) in either the placebo or DMED groups." (page 1127, right column,

line 1 from the bottom to page 1128, left column, line 13)

"Discussion

DMED caused profound sedation with most subjects in the 1.0 and 2.0 /μg/kg groups falling asleep either during or shortly after the infusion. However, increasing the dose of DMED from 1.0 to 2.0 μg/kg did not significantly increase the percentage of subjects falling asleep or increase the average VAS sedation scores but did prolong these effects, indicating that sleep in most undisturbed subjects occurs following a dose of 1.0 μg/kg." (page 1130, left column, lines 3 from the bottom to right column, line 6)

(5) Evidence A No. 5

"Sedation, Analgesia, and Paralysis in the Intensive Care Unit" (Title)

"The intensive care unit (ICU) is an extremely stressful environment where anxiety is prevalent, pain frequent, rest difficult, and sleep often impossible. Relief of pain and anxiety is often neglected while efforts focus on immediate life-threatening concerns. A growing awareness of ICU-imposed stress and the increasing popularity of some modes of mechanical ventilation such as extended ratio ventilation have highlighted the need for effective sedation, analgesia, and occasionally, paralysis.

The goal of therapy is to provide adequate analgesia, sedation, and anxiolysis without causing adverse autonomic or cardiopulmonary consequences. Above all, sedation and paralysis must be used for the comfort and well-being of the patient-not that of the staff. Akin to the operating room setting, a balanced, multidrug approach is usually the best way to maximize patient comfort and minimize side effects. On the rare occasions when it is not possible to relieve discomfort, amnesia is desirable. Nonparalyzed patients should be sedate but sufficiently awake to communicate their needs to nurses and physicians; sedation to unconsciousness is mandated during paralysis. The art of pain control is difficult at best

in this setting, where patient comfort must be balanced against the numerous adverse drug effects. Unfortunately, concerns over safety often cause nurses and physicians to err on the side of insufficient relief of patient discomfort.

The understandable reluctance to sedate patients who are not receiving mechanical ventilation for fear of producing respiratory depression often leaves nonintubated patients anxious and in pain. In addition to the discomfort itself, unrelieved pain can cause splinting that leads to atelectasis. Pain also discourages activity, promoting deep venous thrombosis and deconditioning. While every effort should be made to maximize patient comfort, excessive sedative or analgesic use can produce numerous complications. Excessive sedation causes hypotension and gastrointestinal hypomotility, and masks the occurrence of intercurrent illnesses. Pharmacologic obtundation also reduces tidal volume, vital capacity, and minute ventilation, and inhibits forceful coughing. (page 566, Abstract)

"CHOOSING PHARMACOLOGIC AGENTS

The choice of a sedative or paralytic drug, dosage, and route of administration should be made rationally based upon pharmacologic properties of the drug and individual patient requirements. Three common problems occur with the use of sedative, analgesic, and paralytic drugs in the ICU. Probably the most common error is inadequate use of analgesics, particularly administration of insufficient doses of analgesics on too infrequent a schedule. The second most common problem is the use of ultra-short-acting agents when long-term (days) sedation, analgesia, or paralysis is the goal. Use of short-acting agents theoretically offers the flexibility of rapid interruption of drug effect, but rapid reversal is rarely necessary in the ICU, and undersedation is often the result of using short-acting drugs. When drug effects must be reversed, naloxone promptly interrupts narcotic effects, and flumazenil can counteract benzodiazepine effects. The use of short-acting drugs for long-term indications is also costly, and even short-acting compounds and their metabolites can accumulate in the critically ill when used for hours or days, negating their "short-acting" advantages. The third and an unforgivable error is paralyzing awake patients. This

practice is never acceptable and must be avoided at all cost." (page 566, the right column, lines 9 to 32)

"SEDATIVE-ANXIOLYTIC AGENTS

Benzodiazepin

Benzodiazepines are sedative-anxiolytics that promote amnesia. Of the three drugs most commonly used in the ICU, lorazepam is the most potent amnestic agent, followed by midazolam and diazepam." (page 568, left column, lines 36 to 41)

(6) Evidence A No. 6

"Stress, agitation, and brain failure in critical care medicine" (Title)

"The term 'agitation' describes a syndrome of excessive motor activity, usually nonpurposeful and associated with internal tension. For intensivists, agitation is not so much a diagnosis, but a consequence of more fundamental etilogics that, when expressed, result in disquietude. Agitation is important in the intensive care unit (ICU) because it can alter the diagnosis and course of medical treatment. It can obscure the etiology of underlying disease processes like a smoke screen, making effective diagnosis difficult or impossible. It may result in the inability of the patient to cooperate with monitoring and therapeutics that require him or her to lie relatively still and quiet. Treatment of agitation without consideration of underlying causation gives the false impression of wellness, when in reality end-organ damage is occurring either as a result of agitation itself or as a result of exacerbation of the underlying pathology.

Prior to the technological revolution in critical care medicine, agitation was a relatively minor issue. Little could be done for critically ill patients but to make them as

comfortable as possible and observe them for treatable decompensations. Modern ICUs now have the potential to return critically ill patients to productivity by using technological advances in monitoring and closely titrated care, effectively pinning the patient firmly to the bed with tubes and appliances. As a result of high-tech hemodynamic monitoring and support devices, new kinds of stress have been conferred upon the already hemodynamically unstable patient that he or she never had to deal with before, and simplistic, symptomatic, 'shotgun' sedation no longer applies." (page 52, Abstract)

"Anxiety

The subjective sensation of anxiety is most prevalent during the first 24 hours of ICU tenancy. Many factors contribute to the experience of anxiety, including the fear of death or disability, misunderstanding of information provided by staff, discomfort, and restricted ability to perform usual activities. These factors may be associated with feelings of helplessness and loss of control. In the ICU, anxiety may be characterized by hyperactivity or withdrawal and may not necessarily precipitate a catecholamine response. Anxiety may rapidly progress to delirium, especially in elderly patients who have a decreased ability to cope with unusual stress." (page 59, left column, lines 16 to 32)

"α-2 agonists have been used by anesthesiologists and veterinary surgeons for the last decade as adjuncts to operative anesthesia. This class of drugs, which long ago established itself as antihypertensive, has also been found to possess anxiolytic, sedative, analgesic, and antiemetic properties." (page 62, left column, lines 9 to 15)

"Unfortunately, clonidine is not yet approved for intravenous use in the United States, but IV administration has been investigated in Europe. Postoperative patients who after spinal fusion received a continuous IV infusion of 0.3 mg/kg/hr of clonidine required significantly less supplementary doses of morphine than those not treated with clonidine. Careful titration of IV clonidine as a supplement to analgesics or sedatives in severe agitation syndromes in critical care patients is a new area of clinical investigation.

Other α-2 agonists not currently used in clinical practice have practical potential in

the treatment of severe agitation and delirium. The highly selective α-2 agonist dexmedetomidine reduces anesthetic requirements and improves recovery from anesthesia. The drug was well tolerated, with no significant related side effects. In addition, dexmedetomidine has been shown to produce anxiolytic effects comparable to those of benzodiazepines, but a much less negative effect on hemodynamics." (page 62, right column, line 3 from the bottom to page 63, left column, line 22)

"Treatment of anxiety and discomfort

Several authors recommend that anxiolytic medications be used routinely in the ICU, especially for patients with coronary artery insufficiency who are at risk for agitation-related decompensation. Benzodiazepines have been the mainstay of ICU anxiety treatment for many years because they offer a relatively wide margin of safety from unwanted side effects." (page 63, left column, line 31 to right column, line 1)

(7) Evidence A No. 7

"infusion ...3 Injection, transfusion (intravenous administration of fluid other than blood, e.g. saline solution)." (page 719, right column, lines 10 to 5 from the bottom)

(8) Evidence A No. 8

"managed under intensive care, and sedated during artificial breath and after extubation in patients capable of early extubation" (page 663, line 3)

"Usually, dexmedetomidine is continuously infused to adults intravenously for 10 min at an administration speed of 6 μg/kg/hr (initial loading dose), followed by continuous infusion with a maintenance dose range of 0.2 to 0.7 μg/kg/hr (maintenance dose) so as to achieve the optimal sedation level according to the condition of patient.

It should be noted that the period of administration of the drug must not exceed 24 hours." (page 667, lines 2 to 5)

(9) Evidence A No. 9

"CARDIOPULMONARY BYPASS, MYOCARDIAL MANAGEMENT, AND SUPPORT TECHNIQUES" (Title)

"Holter monitor and ECG recordings. As previously described, perioperative ECG changes were analyzed in two ways.

Continuous recording with a 3-channel Holter monitor. Monitoring began 2 hours after release of the aortic crossclamp in the intensive care unit and lasted for 48 hours (Marquette Holter Recorder, Series 8500)." (page 1463, left column, lines 35 to 41)

(10) Evidence A No. 10

"Cardiovascular Responses during Sedation after Coronary Revascularization" (Title)

"Myocardial Ischemia

All patients were monitored continuously using a three-channel Holter ECG recorder (series 8500, Marquette, Milwaukee, WI) for at least 8 h preoperatively, throughout surgery, and for the entire sedation period." (page 1353, left column, lines 32 to 36)

"The incidence of myocardial ischemia as measured by Holter monitoring was compared in the two treatment groups during the pre-CPB, post-CPB, and ICU sedation periods (Table 6)." (page 1355, the right column, lines 22 to 26)

“In the current study, myocardial ischemia (as defined by Holter ECG monitoring) was detected in only 12-13% of patients in either group during the period of ICU sedation.” (page 1358, left column, lines 12 to 9 from the bottom)

(11) Evidence A No. 11

"Magnesium supplementation in the prevention of arrhythmias in pediatric patients undergoing surgery for congenital heart defects" (Title)

"Experimental design ...

Upon arrival in the ICU, a 2-channel, 5-lead Holter monitor (Marquette Series 8500, Milwaukee, WI) was attached to each patient in the study" (page 2, lines 41 to 42)

(12) Evidence A No. 12

"Time for critically ill patients to regain mobility after early mobilization in the intensive care unit and transition to a general inpatient floor" (Title)

"Purpose: The purpose of this study is to determine if patient mobility achievements in an intensive care unit (ICU) setting are sustained during subsequent phases of hospitalization, specifically after transferring to inpatient floors and on the day of hospital discharge.

Materials and Methods: The study is an analysis of adult patients who stayed in the ICU for 48 hours or more during the second quarter of 2013. The study sample included 182 patients who transferred to a general inpatient floor after the ICU stay.

Results: ... One-third of patients ambulated in the ICU, and those patients had significantly shorter post-ICU and hospital stays compared with patients who did not ambulate in the ICU." (page 1, Abstract)

(13) Evidence A No. 13

"For the above reason, the applicant replied that the desensitization of centrally acting α2 receptor was unlikely to occur in a clinical use of the drug in view of the fact that, in addition to the result of clonidine in human, there was also a report that the attenuation of sedation effects was not observed when 100 μg/kg (ip) of the drug was administered after the administration of 1 μg/kg/hr of the drug was administered to a rat for 7 days, whereas sedation effects were attenuated when sustained administration was conducted at a dose of 3 μg/kg/hr or more (Reid K et al, Pharmacol Biochem Behav, 47:171-175, 1994), and the clinically maintained dose of the drug is 0.2 to 0.7 μg/kg/hr and the administration is completed by 24 hours." (page 16, lines 6 to 2 from the bottom)

(14) Evidence A No. 14

"Clonidine as a sedative adjunct in intensive care" (Title)

"We used clonidine as a sedation adjunct for several intensive care patients." (page 265, left column, main text, lines 4 to 5)

(15) Evidence A No. 15

"Postoperative Pharmacokinetics and Sympatholytic Effects of Dexmedetomidine" (Title)

"Dexmedetomidine is a selective α2-adrenoceptor agonist with centrally mediated sympatholytic, sedative, and analgesic effects. This study evaluated: 1) pharmacokinetics of dexmedetomidine in plasma and cerebrospinal fluid (CSF) in surgical patients; 2) precision of a computer-controlled infusion protocol (CCIP) for dexmedetomidine during the immediate postoperative period; and 3) dexmedetomidine's sympatholytic effects during that period. Dexmedetomidine was infused postoperatively by CCIP for 60 min to eight patients, targeting a plasma concentration (Cp) of 600 pg/mL." (page 1136, Abstract, left column, lines 1 to 12)

"Dexmedetomidine is a selective α2-adrenoceptor agonist. In healthy volunteers and in

surgical patients, it has sedative, analgesic, and anesthetic-sparing effects, and it decreases heart rate, blood pressure, and circulating plasma catecholamines in a dose-dependent fashion." (page 1136, Abstract, left column, lines 1 to 6)

"The study was an open trial using a single dose of dexmedetomidine, which was administered for 60 min after surgery by a CCIP, targeting a plasma concentration of 600 pg/mL. ... (omitted) ... The dexmedetomidine infusion was started approximately 30 min after the patient's arrival in the postanesthesia care unit once blood pressure and heart rate varied <30% over a 5-min period." (page 1137, left column, lines 24 to 38)

(16) Evidence A No. 16

"POSTANESTHESIA CARE UNITS" (Title)

"Purpose of the PACU

In contrast to the older practice of returning patients directly from the operating table to their ward beds, the PACU allows centralization of care by a group of specially trained nurses who are expert in interpreting and responding to the events of the brief but intense period immediately following a procedure requiring anesthesia. The PACU has highly specialized facilities, and essentially functions as an intensive care unit (ICU). This is appropriate, since all patients who enter a PACU face some type of threat or danger to their lives. Furthermore, the immediate proximity of the PACU to the OR is critical because it provides instant access to essential resources, including supplies and equipment, but even more importantly, the surgical and anesthesia personnel who recently cared for the patient. This immediate availability allows timely intervention and treatment of any significant problems during the immediate postsurgical period." (page 57, line 6 from the bottom to page 58, line 6)

(17) Evidence A No. 17

"The Importance of Tools in Specific Nursing Care in the Post-Anesthesia Care Unit (PACU)" (Title)

"This unit is located next to the operation room (OR) and it is considered to be one of the most dangerous stages of anesthesia. The goal of PACU is to provide the patients under general anesthesia or Local anesthesia with necessary cares. Monitoring of the level of consciousness, reflexes of airway, and controlling the vital signs are some of the nursing cares in PACU. Frouliti believes that the nature of PACU is actually providing nursing care. PACU is a place where the patients are in a critical state and require intensive care." (page 1, left column, lines 7 to 14)

No. 5 Judgment by the body

The collegial body determines that it cannot be said that the patent should be invalidated by the Invalidation Reasons 1 and 2, for the following reasons:

For reference, in the following, Evidence A No. 1 and the following evidences are also referred to as A1, A2, ... in this order.

1 Invalidation Reason 1 (Lack of novelty)

(1) Regarding "sedating a critically ill patient who is given intensive care" of the patent invention

In the patent invention, dexmedetomidine or a pharmaceutically acceptable salt thereof (hereinafter collectively referred to "dexmedetomidine") is used for "sedating a critically ill patient who is given intensive care."

The above "sedating a critically ill patient who is given intensive care" used herein means "sedation" of "a critically ill patient who is given intensive care." The criteria to distinguish "a critically ill patient" from patients other than the critically ill patient such as a moderately symptomatic patient or a mildly symptomatic patient varies depending on the distinction of illness or injury, diseased organ, a degree of disease progression and the selection of treatment method, etc. In view of this, it cannot be said that a person skilled in the art could unambiguously understand the meaning of the above term specifying the use

of the patent invention of "sedating a critically ill patient who is given intensive care" from the recitation of the Claims.

Accordingly, in advance of consideration of the invalidation reason against the patent invention, the meaning of term of the above "sedating a critically ill patient who is given intensive care" is construed in view of the description of the patent specification.

The patent specification has the following description with respect to "sedating a critically ill patient who is given intensive care":

(A) "[0001]

[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."

(B) "[0002]

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."

According to the description (A) of the patent specification, the patent specification discloses that "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."

In view of this, "sedating a critically ill patient who is given intensive care" of the patent invention may be construed as including the treatment of "the conditions that may affect the patient's comfort, such as pain and anxiety in the ICU context" in addition to "the actual sedation of a patient in the ICU."

Further, according to the description (B) of the patent specification, subsequent to the above description (A), the patent specification discloses that "Patients recovering from an episode of critical illness have reported factors they found most distressing during their ICU stay ... 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."

In view of this, the above "the conditions that may affect the patient comfort, such as pain and anxiety in the ICU context" means "the treatment of anxiety, pain, fatigue, weakness, thirst, the presence of various catheters, and minor procedures such as physiotherapy." The above treatment of "conditions" means having the above patients free of "unpleasant memories" against the above "conditions," and to achieve this, "ensuring that the patient is comfortable, relaxed, and tolerates uncomfortable procedures such as placement of iv-lines or other catheters, but is still arousable."

Further, the above patients may have "unpleasant memories" against "the conditions that may affect the patient comfort, such as pain and anxiety in the ICU context" or have necessity to "be comfortable, relaxed, and tolerate uncomfortable procedures such as placement of iv-lines or other catheters, but [are] still arousable" just because the above patients may sometimes be awake during the stay at intensive care unit (ICU), and then undergo "the conditions that may affect the patient's comfort, such as pain and anxiety in the ICU context."

Consequently, as a result, the use of "sedating a critically ill patient who is given intensive care" of the patent invention is construed as the use of "sedation including the treatment of the conditions that may affect the patient's comfort, such as pain and anxiety in the ICU context, including anxiety, pain, fatigue, weakness, thirst, the presence of various catheters, and minor procedures such as physiotherapy in addition to the actual sedation of the patient in the ICU."

(2) Determination of Invalidation Reason 1 (Lack of novelty)

Demandant argues that the inventions 1 to 4 are identical to the inventions described in Evidence A No. 1, and thus these inventions are not patentable under the provision of Article 29(1)(iii) of the Patent Act, and as a consequence, the patents for these inventions correspond to the patents specified in Article 123(1)(ii) of the Patent Act and thus should be invalidated.

It cannot be said, however, that A1 discloses the use of "sedating a critically ill patient who is given intensive care" of the patent invention; i.e., the use of "sedation including the treatment of the conditions that may affect the patient's comfort, such as pain and anxiety in the ICU context, including anxiety, pain, fatigue, weakness, thirst, the presence of various catheters, and minor procedures such as physiotherapy which the above patients undergo when they may sometimes be awake during the stay at intensive care unit (ICU), in addition to the actual sedation of the patient in the ICU."

Consequently, it cannot be said that the patent inventions 1 to 4 are the inventions described in A1.

The reason is set forth below.

A1 discloses the following matters. Since the original text is in English, the Japanese translation is described:

(A1a) "Effects of Perioperative Dexmedetomidine Infusion in Patients Undergoing Vascular Surgery" (Title)

(A1b) "Background: Dexmedetomidine is a highly selective α_2-adrenergic agonist, and in

healthy patients improves preoperative, perioperative, or postoperative (perioperative) hemodynamic stability, whereas it decreases blood pressure and heart rate. The purpose of the test was to preliminarily evaluate the hemodynamic action of Dexmedetomidine to be administered preoperatively, perioperatively, or postoperatively in patients at high risk for coronary arteriopathy.

Method: To twenty-four patients undergoing vascular surgery continuously infused was placebo or one unit of three dosages of dexmedetomidine; i.e., targeted plasma concentrations of 0.15 ng/ml (low-dose), 0.30 ng/ml (medium-dose), or 0.45 ng/ml (high-dose) from 1 h before induction of anesthesia throughout the intraoperative period and for 48 h postoperatively. All the patients were subjected to a standard anesthesia and hemodynamics were monitored. Blood pressure, heart rate, and Holter electrocardiogram were monitored, and further the monitoring of preoperative continuous 12-Lead ECG, perioperative anesthetic level and regional wall motion (UCG), and postoperative cardiac enzyme were added.

Result: Preoperatively, in dexmedetomidine dose patients, decrease in heart rate (low-dose 11%, medium-dose 5%, high-dose 20%) and decrease in systolic blood pressure (low-dose 3%, medium-dose 12%, high-dose 20%) were observed. Intraoperatively, a greater amount of vascular agonist was required in the dexmedetomidine dose group to maintain hemodynamics within a certain range. Postoperatively, the dexmedetomidine groups had significantly less tachycardia than the placebo group (minutes/monitored hours) (placebo 23 minutes/hr; low-dose 9 minutes/hr, $P = 0.006$; medium-dose 0.5 minutes/hr, $P = 0.004$; high-dose 2.3 minutes, $P = 0.004$). In any group, bradycardia was rarely observed. No myocardial infarction identifiable trend in clinical test result was observed.

Conclusion: The infusion of dexmedetomidine up to the targeting plasma concentration of 0.45 ng/ml appeared to be beneficial in perioperative hemodynamic management of patients undergoing vascular surgery but required greater intraoperative pharmacologic intervention to support blood pressure and heart rate.

(Key words: Dexmedetomidine: hemodynamics. Dose-effect. Heart: coronary artery disease. Sympathetic nervous system, α2-adrenergic agonist: dexmedetomidine)" (page 620, Abstract)

(A1c) "Surgical and postoperative stress evoke an endocrine response that manifests as stimulation of the hypothalamus-pituitary-adrenal axis, the renin-angiotensin axis, and the sympathetic nervous system. Stimulation of the sympathetic nervous system increases the levels of circulating plasma norepinephrine and epinephrine, increasing blood pressure and heart rate and the incidence of postoperative complications. The hyperdynamic changes predispose the myocardium to ischemia, especially in the patient population with decreased reserve for coronary blood flow. Preoperative, perioperative, and postoperative ischemia are associated with a significant increase in postoperative morbidity and mortality. Attenuating the preoperative, perioperative, and postoperative stress response could decrease the incidence of myocardial ischemia and thereby reduce the incidence of preoperative, perioperative, and postoperative morbidity and mortality in patients at high risk for myocardial ischemia.

Several clinical studies suggest that α2-adrenergic agonists might be effective in blunting the perioperative stress response and that clonidine may have perioperative antiischemic effects. Dexmedetomidine is an α2-adrenergic agonist with a 10-fold greater α2/α1-receptor selectivity than clonidine. In healthy volunteers, dexmedetomidine decreases circulating catecholamines by up to 90% and, like clonidine, has antinociceptive and sedative effects. In healthy surgical patients, dexmedetomidine increases hemodynamic stability, decreases anesthetic requirements, and blunts the hyperdynamic response to intubation. The sympatholysis also results in potentially adverse clinical effects, such as a decrease in blood pressure and bradycardia. Such hemodynamic changes might not be tolerated by patients with vascular disease or severe myocardial disease.

Thus far, dexmedetomidine has been administered only to healthy volunteers and healthy surgical patients. Therefore, to perform a preliminary evaluation of the feasibility and effects of preoperative, perioperative, and postoperative administration of dexmedetomidine in high-risk surgical patients, we studied three consecutively increasing doses of an infusion of dexmedetomidine in vascular surgery patients, a population with a high incidence of coronary artery disease (CAD) who might benefit significantly from increased preoperative, perioperative and postoperative hemodynamic stability.

Methods

Patients

With approval from our Human Research Committee and written informed consent,

we studied 25 patients with or at high risk for CAD who were scheduled for vascular surgery at the San Francisco Veterans Affairs Medical Center. Study entry criteria included one or more of the following: a history of classic angina pectoris; a history of myocardial infarction; electrocardiographic (ECG) evidence of Q waves typical of infarction without a history; CAD detected by angiography; or the presence of two or more risk factors for CAD, including cigarette smoking, treatment for hypertension, treated diabetes mellitus, or hypercholesterolemia (> 240 mg/dL). Excluded from study were patients with unstable angina, uninterpretable preoperative ECGs (left bundle branch block), patients taking clonidine or tricyclic antidepressants, and those who did not receive the study drug continuously for at least the first 24 postoperative hours. Cardiac medications were continued until the night of surgery.

Experimental Protocol

The study was a double-blind, randomized, dose-escalation trial using three different doses of dexmedetomidine and placebo. Twenty-four patients were divided into three groups of eight to form low-, medium-, and high-dose test groups, each having six patients who received dexmedetomidine and two who received placebo. Thus, six patients received placebo during the study. The number of patients used in this study was not based on power calculations. Study began with the low-dose group, and once this dose was determined to be tolerable, proceeded to the medium-dose group, then, after the same determination, the high-dose group. Initially, 25 patients were enrolled in the study, but one subject (high-dose group) was excluded when dexmedetomidine was discontinued within 24 h of administration in order to permit an emergent return to surgery.

Dexmedetomidine was administered by a computer-controlled infusion pump (CCIP) targeting plasma concentrations of 0.15 ng/ml (low-dose), 0.30 ng/ml (medium-dose), and 0.45 ng/ml (high-dose). STAN-PUMP software (Steve Shafer, Stanford University, Palo Alto, CA) was used to run the infusion pump (Harvard Apparatus 22, Harvard Apparatus, South Natick, MA). The STANPUMP software updated the infusion rate at 10-s intervals using dexmedetomidine pharmacokinetic data to allow drug delivery to targeted plasma concentrations. The infusion rate data were stored in a laptop computer, which was used to run the STANPUMP program. To study the effect of dexmedetomidine in awake and anesthetized patients, infusion was begun 1 h before induction of anesthesia

and continued throughout the intraoperative period and for 48 h postoperatively. The average amount of dexmedetomidine infused was 2.64 micro gram/kg (range 2.30-3.75 micro gram/kg), 5.31 micro gram/kg (range 4.40-5.97 micro gram/kg), and 8.03 micro gram/kg (range 5.57-9.87 micro gram/kg) for the low-, medium-, and high-dose groups, respectively. Patients were not permitted to ambulate during study drug infusion." (page 620, right column, line 12 to page 621, right column, line 28)

(A1d) "Postoperative Analgesia

Postoperative analgesia was provided by intravenous morphine sulfate, delivered by a patient-controlled analgesia (PCA) pump. The initial PCA setting was a 1-mg bolus dose with a lock-out interval of 6 min. For inadequate analgesia, additional 2-mg doses of morphine were administered intravenously as needed. If analgesia remained inadequate after the additional 2-mg bolus doses, the PCA dose was increased in increments of 0.5 mg.

Analgesia was assessed using a visual analog scale (VAS), comprising a 100-mm horizontal line with one pole representing "no pain" and the other "worst pain imaginable." The scale was administered every 4 h postoperatively for the first 48 h, as long as the patient was awake. Patients assessed their pain at rest and rated the severity of the worst pain since the last assessment." (page 623, right column, line 5 from the bottom to page 624, left column, line 12)

(A1e) "Sedation and Analgesia

After the 1-h infusion preceding induction of anesthesia, all patients in the medium- and high-dose groups fell asleep but were easily arousable. During the second postoperative day, there was no clinically observable sedation from the study drug. Postoperative VAS pain scores were similar among groups, and postoperative morphine requirements did not differ." (page 627, the right column, lines 25 to 32)

(A1f) "The current study evaluated, in a preliminary manner, the effects of dexmedetomidine in high-risk patients undergoing vascular surgery. This study also is the first to administer dexmedetomidine as a continuous perioperative infusion over a 2-day

period to cover the duration of the majority of perioperative stress and hemodynamic lability. Our results suggest that a perioperative dexmedetomidine infusion up to a targeted plasma concentration of 0.45 ng/ml can be used in high-risk vascular surgical patients if other drugs are given to offset the depression of heart rate and blood pressure." (page 628, left column, lines 8 to 19)

(A1g) "Anesthetic Requirements and Sedation

Aho et al. reported that a continuous intraoperative dexmedetomidine infusion can decrease the requirements for isoflurane by up to 90% in healthy patients. Our intraoperative use of alfentanil and nitrous oxide provided sufficient anesthesia for our vascular surgery patients, such that isoflurane requirements were low in all groups. Therefore, we cannot evaluate the potential reductive effect of dexmedetomidine on anesthetic requirements in vascular surgery patients. A study with minimal background anesthesia will be required to achieve this.

Several studies have reported dose-dependent sedative effects with dexmedetomidine. During the 1-h dexmedetomidine infusion preceding induction of anesthesia, the patients in our medium- and high-dose groups fell asleep but were easily arousable. Although the dexmedetomidine infusion had a sedative effect before induction, sedation was not observable the day after surgery. This is consistent with recent findings of tachyphylaxis to the anesthetic effects of dexmedetomidine in rats." (page 630, right column, line 6 from the bottom to page 631, left column, line 16).

(A1h) "Conclusion

The hemodynamic effects of dexmedetomidine in vascular surgery patients appear to be similar to those in healthy volunteers. A dose of 0.45 ng/ml appeared to be most effective in blunting hemodynamic responses to perioperative stress but required greater intraoperative pharmacologic intervention to support blood pressure and heart rate. Further studies in a larger number of high-risk patients will be conducted to verify these preliminary results." (page 632, left column, lines 22 to 31)

It can be seen from A1a and A1b that A1 is a document reporting that the dexmedetomidine dose up to a target plasma level of 0.45 ng/ml seems to be beneficial to the hemodynamics management of perioperative surgical patient undergoing vascular surgery, while the patients required more pharmacological intervention in operation to support blood pressure and heart rate as a result of preliminary evaluation of the effects on hemodynamics of perioperative dose of dexmedetomidine in surgical patients at a high risk for coronary artery disease. Further, the first to third paragraphs of A1c suggest that patients undergoing vascular surgery are in a patient group that is believed to have high morbidity rate of coronary artery disease, and receive a greater benefit from the increase in perioperative hemodynamic stability. Further, "Experiment protocol" of A1c shows that, to study the effect of dexmedetomidine in awake and anesthetized patients, infusion was begun 1 h before the induction of anesthesia and continued throughout the intraoperative period and for 48 h postoperatively. A1d and A1e show that postoperative VAS pain scores were similar among groups, and postoperative morphine requirements did not differ; i.e., postoperative analgesic effects can be seen in any dose group. Similarly, A1d and A1e suggest that sustained dose of dexmedetomidine had a sedative effect before the induction of anesthesia, whereas the sedation was not observed the day after surgery. Further, it cannot be seen from the other description of A1 pointed out by the Demandant that dexmedetomidine was administered to a person other than the above surgical patients undergoing vascular surgery.

Consequently, A1 only discloses the use of dexmedetomidine for hemodynamic stabilization of perioperative surgical patients undergoing vascular surgery and having high risk for coronary artery disease, sedation of the patients before induction, and postoperative analgesia of the patients. It cannot be said that A1 discloses the use of "sedating a critically ill patient who is given intensive care" of the patent invention; i.e., the use of "sedation including the treatment of the conditions that may affect the patient's comfort, such as pain and anxiety in the ICU context, including anxiety, pain, fatigue, weakness, thirst, the presence of various catheters, and minor procedures such as physiotherapy which the above patients undergo when they may sometimes be awake during the stay at intensive care unit (ICU), in addition to the actual sedation of the patient in the ICU." Therefore, it cannot be said that the patent inventions 1 to 4 are described in A1.

Therefore, the patents according to the patent inventions 1 to 4 cannot be

invalidated on the ground of invalidation reason 1 (lack of novelty) as in the demandant's argument.

(3) Determination of Invalidation Reason 2 (Lack of inventive step)

a. The Invalidation Reason 2 (Lack of inventive step) argued by Demandant is generally as follow.

(a) The patent invention 1

(a-1) The comparison of the patent invention 1 with cited invention 1

Evidence A No. 1 discloses the cited invention 1 of

"a: for the perioperative use in high-risk vascular surgical patients,

b: Use of dexmedetomidine in the manufacture of a pharmaceutical

e: wherein dexmedetomidine is, in an amount that reaches plasma concentration of 0.15 ng/ml to 0.45 ng/ml,

f: administered to a human."

Comparing the patent invention 1 and cited invention 1, these inventions have common ground in the use of dexmedetomidine for the manufacture of pharmaceutical product (constituent element B), whereas they differ from each other in the following point:

<The different feature 1>

The patient of the patent invention 1 is "a critically ill patient who is given intensive care," whereas the vascular surgical patients of cited invention 1 are not definitely described as critically ill patients subjected to intensive care postoperatively (constituent element A).

<The different feature 2>

In the patient invention 1, dexmedetomidine is administered for the sedation of

postoperative patients, whereas in the cited invention 1 dexmedetomidine is administered for the preliminary evaluation of its perioperative hemodynamic effects, but not for the sedation of postoperative patients (constituent element A).

<The different feature 3>

In the patent invention 1, patients are arousable and oriented, whereas the cited invention 1 is silent about this point (constituent element C).

The patent invention 1 is substantially identical to the cited invention 1; however, given the above different features 1 to 3, it is considered as to whether or not the patent invention 1 is easily conceivable on the basis of the cited invention 1.

(a-2) Examination on Different Features

A Regarding the different feature 1

Different feature 1 is that the patient of the patent invention 1 is "a critically ill patient who is given intensive care," whereas the vascular surgical patients of cited invention 1 are not definitely described as critically ill patients subjected to intensive care postoperatively (constituent element A).

Evidence A No. 6 discloses that it is an important problem in the ICU to dispel anxiety, and benzodiazepine has been used as a sedative drug for a long time, and that dexmedetomidine has anti-anxiety action comparable to that of benzodiazepine, and less side effects that affect hemodynamics. Evidence A No. 5 also discloses that it is important in the ICU to remove anxiety as well as pain, and it is necessary to make patients sufficiently arousable for communication, while sedating. Evidence A No. 6 also discloses that the patient is required to lie relatively still and quiet in order to cooperate with monitoring and therapeutics in the ICU. Further, as is shown in Evidence A No. 3 and Evidence A No. 4, it is well-known that dexmedetomidine is a dose-dependent sedative drug and capable of causing patients to completely fall asleep with increasing doses, whereas it may also control patients so as to be easily arousable with adjusted doses and have effects of alleviating anxiety.

Therefore, even though the cited invention 1 does not disclose the use of dexmedetomidine in an intensive care unit, a person skilled in the art could have easily conceived of the use of dexmedetomidine for critically ill patients in the ICU on the basis of the postoperative use of dexmedetomidine for patients undergoing vascular surgery in the cited invention 1.

B Regarding the different feature 2

Different feature 2 is that, in the patent invention 1, dexmedetomidine is administered for the sedation of postoperative patients, whereas in the cited invention 1 dexmedetomidine is administered for the preliminary evaluation of its perioperative hemodynamic effects, but not for the sedation of postoperative patients (constituent element A).

In the patent invention 1, as already discussed, "sedation" includes the action of alleviating anxiety. Dexmedetomidine is well-known as a sedative drug for alleviating anxiety action (anti-anxiety action) (Evidence A No. 3, Evidence A No. 4, and Evidence A No. 6). Cited invention 1 also discloses the use of dexmedetomidine for the treatment of postoperative stress.

Further, as aforementioned, it is well-known according to Evidence A No. 5 and Evidence A No. 6 that the sedation including alleviation of anxiety action is required in the ICU.

Therefore, a person skilled in the art could have easily conceived of using dexmedetomidine for sedation including the meaning of alleviating anxiety in the ICU in the cited invention 1.

C Regarding the different feature 3

Different feature 3 is that, in the patent invention 1, patients are arousable and oriented, whereas the cited invention 1 is silent about this point (constituent element C).

As aforementioned, Evidence A No. 5 discloses that patients are required to be arousable sufficient to convey their own requests to nurses and doctors in the ICU, while sedated.

Further, Evidence A No. 6 also discloses that patients are required to lie relatively still and quiet to cooperate with monitoring or therapeutics in the ICU. Specifically, it is well-known that patients are desirably arousable and in an oriented condition to cooperate with therapeutics, although the sedation is necessary in ICU. Further, it is well-known that dexmedetomidine is dose-dependent for sedation and capable of causing patients to be easily arousable by the adjustment of dosage amount (Evidence A No. 3 and Evidence A No. 4).

Therefore, a person skilled in the art could have easily conceived of using dexmedetomidine so as to cause patient to be arousable and oriented by adjusting the dosage amount in the cited invention 1.

(a-3) Summary

As seen above, the effects of the patent invention 1 are not definitely described as effects in the specification. Even if the effects were "the ICU sedation in an oriented condition" in view of the description in the paragraph [0027], dexmedetomidine is well-known as a sedation drug that makes patients easily arousable by the adjustment of dosage amount (Evidence A No. 3 to Evidence A No. 6). Thus the effects may be expected by a person skilled in the art.

Therefore, a person skilled in the art could have easily conceived of the patent invention 1 on the basis of cited invention 1 and well-known techniques.

(b) As for the Patent Inventions 5 and 6

(b-1) The comparison of the patent invention 5 or the patent invention 6 with cited invention 1

The patent invention 5 comprises the constitution of administering a loading dose or a maintenance dose of dexmedetomidine, and the patent invention 6 further limits the above constitution to be administered to a human. Cited invention 1 is to be administered to a human, however, it is silent about a loading dose or a maintenance dose to be administered.

Therefore, there is the following different feature between the patent invention 5 or

the patent invention 6 and cited invention 1:

<The different feature 4>

In the patent invention 5 and the patent invention 6, dexmedetomidine is administered in two steps of loading dose and maintenance dose, whereas the cited invention 1 did not conduct loading dose (constituent element G).

(b-2) Consideration on the Difference 4

A In general, perioperative sedative drug or analgesics are subjected to loading dose (bolus) according to the urgency and degree of the sedation and analgesia. For example, Evidence A No. 1 describes the bolus dose of morphine for postoperative analgesia.

Further, as aforementioned, Evidence A No. 2 describes the following cited invention 2 with respect to the two-step dose of intraoperative dexmedetomidine:

"a: for the intraoperative use in patients undergoing abdominal hysterectomy

b: Use of dexmedetomidine in the manufacture of pharmaceutical

e: wherein dexmedetomidine is, in an amount that reaches plasma concentration of 0.5 ng/ml to 1.1 ng/ml,

f: intravenously administered,

g: wherein a loading dose and a maintenance dose of dexmedetomidine are administered,

h: wherein the loading dose and the maintenance dose are to be administered to a human,

i: wherein the loading dose of dexmedetomidine is 1.2 to 2.7 μg/kg,

j: wherein the loading dose is administered in 10 minutes,

k: wherein the loading dose of dexmedetomidine is 1.2 μg/kg,

l, m, n: wherein the maintenance rate of dexmedetomidine is 0.36 to 0.81 μg/kg/h."

B As discussed in the item "B Regarding the different feature 2" of the patent invention 1, it is easy to use dexmedetomidine for sedation in the postoperative ICU of the cited invention 1. In the postoperative ICU, it is a design matter for a person skilled in the art to conduct a loading dose as necessary in an attempt to quickly achieve the sedative effects. It should be noted that bolus dose does not change drug efficacy but only causes difference in time until the onset of the drug efficacy.

(b-3) Summary

As described above, the invention 5 and the invention 6 were easily conceivable by a person skilled in the art on the basis of cited inventions 1 and 2 in view of well-known technique.

B The collegial body determines, however, that the patent of the patent invention may not be invalidated on the ground of the Invalidation Reasons 2 (lack of inventive step), for the following reasons:

(a) The demandant's argument in the item (a) of A is summarized as below: a person skilled in the art could have easily conceived of the patent invention 1 on the basis of cited invention 1 and well-known techniques (A3 to A6).

Accordingly, a consideration is given to this; as is discussed above, A1 is a document reporting that the dexmedetomidine dose up to a target plasma level of 0.45 ng/ml seems to be beneficial to the hemodynamics management of perioperative surgical patient undergoing vascular surgery, while the patients required more pharmacological intervention in operation to support blood pressure and heart rate as a result of preliminary assessment of the effects on hemodynamics of dexmedetomidine dose in perioperative surgical patients with high risk for coronary artery disease. A1 only discloses the use of dexmedetomidine for hemodynamic stabilization of perioperative surgical patients undergoing vascular surgery and having high risk for coronary artery disease, sedation of the patients before induction, and postoperative analgesia of the patients. It cannot be said that A2 discloses the use of "sedating a critically ill patient who is given intensive care" of the patent invention; i.e., the use of "sedation including the treatment of the conditions that may affect the patient's comfort, such as pain and anxiety in the ICU context, including

anxiety, pain, fatigue, weakness, thirst, the presence of various catheters, and minor procedures such as physiotherapy which the above patients undergo when they may sometimes be awake during the stay at intensive care unit (ICU), in addition to the actual sedation of the patient in the ICU," nor the description suggesting the use.

In addition, Demandant argues in the above "Regarding the different feature 2" that "Cited invention 1 also describes the use of dexmedetomidine for the treatment of postoperative stress." The postoperative stress used herein is construed as meaning the response of patients' bodies against invasion to the body through operation, but is not construed as the conditions that may affect the patient's comfort, such as pain and anxiety in the ICU context, in view of the description of A1c that "Surgical and postoperative stress evoke an endocrine response that manifests as stimulation of the hypothalamus-pituitary-adrenal axis, the renin-angiotensin axis, and the sympathetic nervous system. Stimulation of the sympathetic nervous system increases the levels of circulating plasma norepinephrine and epinephrine, increasing blood pressure and heart rate and the incidence of postoperative complications. The hyperdynamic changes predispose the myocardium to ischemia, especially in the patient population with decreased reserve for coronary blood flow. Preoperative, perioperative, and postoperative ischemia are associated with a significant increase in postoperative morbidity and mortality. Attenuating the preoperative, perioperative, and postoperative stress response could decrease the incidence of myocardial ischemia and thereby reduce the incidence of preoperative, perioperative, and postoperative morbidity and mortality in patients at high risk for myocardial ischemia."

Further, none of A3 to A5 has a description of using dexmedetomidine for the above use or a description suggesting the use. However, A6 has the following descriptions.

(A6a)

"Stress, agitation, and brain failure in critical care medicine" (page 52, Title part)

(A6b)

The term "agitation" describes a syndrome of excessive motor activity, usually nonpurposeful and associated with internal tension. For intensivists, agitation is not so much a diagnosis, but a consequence of more fundamental etilogics that, when expressed, result in disquietude. Agitation is important in the intensive care unit (ICU) because it can

alter the diagnosis and course of medical treatment. It can obscure the etiology of underlying disease processes like a smoke screen, making effective diagnosis difficult or impossible. It may result in the inability of the patient to cooperate with monitoring and therapeutics that require him or her to lie relatively still and quiet. Treatment of agitation without consideration of underlying causation gives the false impression of wellness, when in reality end-organ damage is occurring either as a result of agitation itself or as a result of exacerbation of the underlying pathology." (page 52, Abstract, lines 1 to 22)

(A6c)

"The subjective sensation of anxiety is most prevalent during the first 24 hours of ICU tenancy. Many factors contribute to the experience of anxiety, including the fear of death or disability, misunderstanding of information provided by staff, discomfort, and restricted ability to perform usual activities. These factors may be associated with feelings of helplessness and loss of control. In the ICU, anxiety may be characterized by hyperactivity or withdrawal and may not necessarily precipitate a catecholamine response. Anxiety may rapidly progress to delirium, especially in elderly patients who have a decreased ability to cope with unusual stress." (page 59, left column, lines 17 to 32)

(A6d)

"α-2 Agonists have been used by anesthesiologists and veterinary surgeons for the last decade as adjuncts to operative anesthesia. This class of drugs, which long ago established itself as antihypertensive, has also been found to possess anxiolytic, sedative, analgesic, and antiemetic properties." (page 62, left column, lines 9 to 15)

(A6e)

"Other α-2 agonists not currently used in clinical practice have practical potential in the treatment of severe agitation and delirium. The highly selective α-2 agonist dexmedetomidine reduces anesthetic requirements and improves recovery from anesthesia. The drug was well tolerated, with no significant related side effects. In addition, dexmedetomidine has been shown to produce anxiolytic effects comparable to those of

benzodiazepines, but a much less negative effect on hemodynamics." (page 63, left column, lines 11 to 22)

(A6f)

"Benzodiazepines have been the mainstay of ICU anxiety treatment for many years, because they offer a relatively wide margin of safety from unwanted side effects." (page 63, left column, lines 4 from the bottom to right column, line 1)

First of all, however, A6 is an academic article, and a document intended to disclose leading-edge technology as of the publication. Therefore, the described content might be said as the content publicly known as of the priority date of the patent invention, and, it cannot be said that it was the common technical knowledge as of the priority date of the patented invention. Consequently, as long as the invalidation reason is premised on the fact that the content of A6 is well-known art before the priority date, the patent of the patent invention may not be invalidated for the invalidation reason.

Furthermore, even if a person skilled in the art who read A1 also read A6 and recognized that the above content of A6 was well-known art as of the priority date, it cannot be said that the patent invention was conceivable without particular creativity by a person skilled in the art on the basis of the cited invention 1 and well-known art as the demandant argues.

Specifically, as aforementioned, A1 is a document reporting that the dexmedetomidine dose up to a target plasma level of 0.45 ng/ml seems to be beneficial to the hemodynamics management of perioperative surgical patient undergoing vascular surgery, while the patients required more pharmacological intervention in operation to support blood pressure and heart rate as a result of preliminary assessment of the effects on hemodynamics of dexmedetomidine dose in perioperative surgical patients with high risk for coronary artery disease. A1 only discloses the use of dexmedetomidine for hemodynamic stabilization of perioperative surgical patients undergoing vascular surgery and having high risk for coronary artery disease, sedation of the patients before induction, and postoperative analgesia of the patients. Thus it is a document with a content totally different from the treatment of anxiety with dexmedetomidine in the ICU.

On the other hand, A6 is directed to stress, agitation, and brain failure in critical

care medicine as in the title in view of A6a. It is definitely different from A1.

Consequently, first of all, it is hard to think that a person skilled in the art who read A1 and tried to make a new invention from the invention described in A1 would refer to A6 with a content totally different from A1. Furthermore, it cannot be said that one could read A6 consisting of as many as 20 pages for main text, and pick out and focus on the description of the above A6b to A6f, and have an inspiration of using dexmedetomidine for the treatment of anxiety in ICU, and combine this suggestion with A1 having a content totally different from the treatment of anxiety in ICU, and conceive of the patent invention on the basis of the invention described in A1 without particular creativity. It is just a matter of hindsight in light of the patent invention to find that the idea could be obtained without particular creativity.

Therefore, it cannot be said that the patent invention was conceivable without particular creativity by a person skilled in the art on the basis of the cited invention and well-known art as the demandant argues.

(b) Subsequently, when consideration is given to the effects of the patent invention, the patent specification has the following description:

(C) "[0006]

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."

(D) "[0027]

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. ... 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."

(E) "[0031]

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 a standard syringe pump and iv administration sets.

[0032]

Twelve 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 was 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 within a range of 0.2 to 0.7 μg/kg/h. After the clinical effects of sedation became evident (within approximately 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 Figure 1).

[0033]

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.

[0034]

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 benzodiazepines 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.

[0035]

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.

[0036]

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.

[0037]

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.

[0038]

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

[0039]

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 to be 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).

[0040]

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.

[0041]

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 a 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.

[0042]

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 μg/ml, base) in 0.9 % sodium chloride solution, and it was administered utilizing a standard syringe pump and iv administration sets. 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 within 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.

[0043]

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.

[0044]

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.

[0045]

During Trial 1, Part I, 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 $\alpha 2$-agonists. Further, dexmedetomidine produced no clinically apparent respiratory depression after cessation of assisted ventilation.

[0046]

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.

[0047]

1. An 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.

[0048]

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.

[0049]

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 occurred one hour in the postoperative course. The patient was extubated at approximately 6 hours, and his blood pressure increased again after the dexmedetomidine infusion was discontinued.

[0050]

4. A 55-year-old male patient with a history of alcohol abuse underwent surgery for head and neck cancer. A dexmedetomidine 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.

[0051]

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 300 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.

[0052]

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 occurred 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.

[0053]

The patient was awake, alert, and able to communicate in writing that he wanted the endotracheal tube removed. When the maximum allowable dose of dexmedetomidine, 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.

[0054]

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.

[0055]

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.

[0056]

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.

[0057]

This case illustrates the importance of administrating dexmedetomidine before the analgesics administered pre-ICU have 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.

[0058]

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 PaCO2 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.

[0059]

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. 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 and 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.

[0060]

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.

[0061]

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 of 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 slight amnesia. She had excellent evolution and was very comfortable with her ICU experience.

[0062]

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 Figure 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.

[0063]

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 remainder 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.

[0064]

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.

[0065]

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 had entered the study with established hypertension.

[0066]

The cases described above illustrate the benefits of dexmedetomidine sedation in critically

ill patients. Appropriately sedated, the patients were oriented, physiologically stable, and experienced minimal pain, discomfort, and anxiety. It is current practice to stop sedative drugs during ventilator weaning and after extubation, in order 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."

(F) "[Figure 1]

臨床	達成された鎮静作用のレベル
1	患者の不安、動揺または落ち着かなさ (restless)
2	患者の協力、適応 (orientec)および平静
3	患者は命令に対して応答する
4	眠っている、しかし光の眉間へのタップまたは大きな聴覚的刺激への活発な応答
5	眠っている、光の眉間へのタップまたは大きな聴覚的刺激への緩慢な応答
6	眠っている、応答なし

ラムセイスケール

"

臨床　Clinical score

達成された鎮静作用のレベル　　Level of sedation achieved

患者の不安、動揺または落ち着かなさ　Patient anxious, agitated or restless

患者の協力、適応および平静　　Patient co-operative, oriented, and tranquil

患者は命令に対して応答する　　Patient responds to commands

眠っている、しかし光の眉間へのタップまたは大きな聴覚的刺激への活発な応答

Asleep but with brisk response to light glabellar tap or loud auditory stimulus

眠っている、光の眉間へのタップまたは大きな聴覚的刺激への緩慢な応答
Asleep, sluggish response to light glabellar tap or loud auditory stimulus

眠っている、応答なし　Asleep, no response

ラムセイスケール　Ramsey scale

According to the description (C) of the patent specification, the patent specification discloses that doctors in the ICU prefer their patients to be asleep but easily arousable. According to the description (D) of the patent specification, it discloses that the patients sedated by dexmedetomidine are arousable and oriented, which makes the treatment of the patient easier, and they are able to respond to questions, are aware but not anxious, and tolerate an endotracheal tube well. Further, according to the descriptions (E) and (F) of the patent specification, it is described that patients in the ICU could communicate in an awakened and well-oriented condition when Ramsey sedation score was 4 and in asleep during the sedation with dexmedetomidine, as in, e.g. patients of 7. and 10. of Example 3, or could be calm, well-oriented, and cooperative when Ramsey sedation score was 2 to 3 and awakened during the sedation with dexmedetomidine, as in, e.g. patients of 5. and 15. of Example 3.

It can be said that the patent invention could cause the effects to allow patients sedated by dexmedetomidine during the stay in an intensive care unit (ICU) to be in an awakened and well-oriented condition when asleep, or calm, well-oriented, and cooperative when awakened, and in either case be able to communicate with doctors in the ICU by using dexmedetomidine for the use of "sedating a critically ill patient who is given intensive care"; i.e. the use of "sedation including the treatment of the conditions that may affect the patient's comfort, such as pain and anxiety in the ICU context, including anxiety, pain, fatigue, weakness, thirst, the presence of various catheters, and minor procedures such as physiotherapy which the above patients undergo when they may sometimes be awake during the stay at intensive care unit (ICU), in addition to the actual sedation of the patient in the ICU."

(c) On the other hand, A1 discloses that

"Sedation and Analgesia

After the 1-h infusion preceding induction of anesthesia, all patients in the medium- and high-dose groups fell asleep but were easily arousable." (page 627, the right column, lines 25 to 28),

"During the 1-h dexmedetomidine infusion preceding induction of anesthesia, the patients in our medium- and high-dose groups fell asleep but were easily arousable." (page 631, left column, lines 8 to 11). This description is just an observation result for patient in sustained administration for one hour in advance to the start of anesthesia described in A1. It cannot even be said that a person skilled in the art could have expected from such description the effects to allow patients sedated by dexmedetomidine during the stay at intensive care unit (ICU) to be in an awakened and well-oriented condition when asleep, or calm, well-oriented, and cooperative when awakened, and in either case be able to communicate with doctors in the ICU.

(d) Further, Demandant argues that "The effects of the patent invention 1 are not definitely described as effects in the specification. Even if the effects were 'the ICU sedation in an oriented condition' in view of the description in the paragraph [0027], dexmedetomidine is well-known as a sedation drug that makes patients easily arousable by the adjustment of dosage amount (Evidence A No. 3 to Evidence A No. 6). Thus, the effects may be expected by a person skilled in the art."

A3 and A4 fail to disclose, however, that a person to whom dexmedetomidine was administered is a patient during the stay in the intensive care unit (ICU). Therefore, even if a person skilled in the art who read Evidence As should recognize the contents as well-known techniques, it cannot be said that a person skilled in the art could expect the effects to allow patients sedated by dexmedetomidine during the stay in the intensive care unit (ICU) to be in an awakened and well-oriented condition when asleep, or calm, well-oriented, and cooperative when awakened, and in either case be able to communicate with doctors in the ICU. It is just a matter of hindsight in light of the patent invention to find that such effects can be expected. Further, A6 fails to disclose that dexmedetomidine is a sedative drug allowing patients to be easily arousable by the adjustment of dosage amount. A5 does not describe dexmedetomidine at all. Therefore, a person skilled in the art who read these Evidence As could not expect the above effects even if one should recognize the

contents as well-known art.

Therefore, the patent invention has particularly significant effects beyond the expectation of a person skilled in the art on the basis of the cited invention and well-known art as demandant argues.

(e) The demandant's argument with respect to A2 is as follows: According to the item (b) of A, in the invention 5 and the invention 6, dexmedetomidine is administered in two steps of loading dose and maintenance dose, whereas the cited invention 1 did not conduct loading dose. In this regard, perioperative sedative drug or analgesics are subjected to loading dose (bolus) according to the urgency or degree of the sedation and analgesia. For example, A1 discloses the bolus dose of morphine for postoperative analgesia. In connection with the two step intraoperative dose of dexmedetomidine, A2 discloses the following cited invention 2:

"a: for the intraoperative use in patients undergoing abdominal hysterectomy

b: Use of dexmedetomidine in the manufacture of pharmaceutical

e: wherein, in an amount that reaches a plasma concentration of 0.5 ng/ml to 1.1 ng/ml, dexmedetomidine

f: intravenously administered,

g: wherein a loading dose and a maintenance dose of dexmedetomidine are administered,

h: wherein the loading dose and the maintenance dose are to be administered to a human,

i: wherein the loading dose of dexmedetomidine is 1.2 to 2.7 μg/kg,

j: wherein the loading dose is administered in 10 minutes,

k: wherein the loading dose of dexmedetomidine is 1.2 μg/kg,

l, m, n: wherein the maintenance rate of dexmedetomidine is 0.36 to 0.81 μg/kg/h." Thus it is easy in the postoperative ICU of the cited invention 1 to use dexmedetomidine for sedation. At the time, it is a design matter for a person skilled in the art to conduct a loading dose as necessary in an attempt to rapidly achieve the sedative effects.

Specifically, the demandant's argument about A2 can be summarized that it is a design matter for a person skilled in the art in light of the cited invention 2 of A2 to administer dexmedetomidine in two steps of loading dose and maintenance dose in the patent invention 5 and the patent invention 6.

However, such demandant's argument about A2 is premised on the fact that the patent invention 1 was easily conceivable by a person skilled in the art on the basis of the cited invention 1 and well-known art (A3 to A6). As aforementioned, such premise is not rationalized.

Additionally, A2 is a document that reported the dexmedetomidine infusion for the maintenance of anesthesia in patients undergoing abdominal hysterectomy as in the title, and discloses that the administration of dexmedetomidine decreased the isoflurane requirement by >90%; however, it cannot be said that A2 discloses the use of "sedating a critically ill patient who is given intensive care" of the patent invention; i.e., the use of "sedation including the treatment of the conditions that may affect the patient's comfort, such as pain and anxiety in the ICU context, including anxiety, pain, fatigue, weakness, thirst, the presence of various catheters, and minor procedures such as physiotherapy which the above patients undergo when they may sometimes be awake during the stay at intensive care unit (ICU), in addition to the actual sedation of the patient in the ICU," nor a description suggesting the use.

Therefore, the demandant's argument about A2 cannot be accepted.

(f) Summary

Therefore, the patents according to the patent inventions 1 to 12 cannot be invalidated on the ground of invalidation reason 2 (lack of inventive step) as in the demandant's argument.

No. 6 Closing

As aforementioned, the Patents according to the patent inventions 1 to 12 cannot be invalidated on the basis of the grounds and means of proof argued by Demandant.

The costs in connection with the trial shall be borne by Demandant under the provisions of Article 61 of the Code of Civil Procedure as applied mutatis mutandis to the provision of Article 169(2) of the Patent Act.

Therefore, the trial decision shall be made as described in the conclusion.

April 13, 2017

Chief administrative judge: NAITO, Shinichi

Administrative judge: MAEDA, Kayoko

Administrative judge: YAMAMOTO, Goichi