IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAXTER HEALTHCARE CORPORATION,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 18-303-RGA
	)	
HOSPIRA, INC. and ORION CORP.,	)	
	)	
Defendants.	)	

APPENDIX TO JOINT CLAIM CONSTRUCTION BRIEF

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HOSPIRA, INC., Plaintiff, v. AMNEAL PHARMACEUTICALS LLC, Defendant.	Civil Action No. 15-697-RGA

MEMORANDUM ORDER

Presently before the Court is the issue of claim construction of multiple terms in U.S. Patent Nos. 8,242,158 ("the '158 patent"); 8,338,470 ("the '470 patent"); 8,455,527 ("the '527 patent"); and 8,648,106 ("the '106 patent") (collectively "the patents-in-suit"). The Court has considered the parties' Joint Claim Construction Brief. (D.I. 44).

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting *Phillips*, 415 F.3d at 1324). When construing patent claims, a court considers the literal language of the claim, the patent specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977–80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Of these sources, "the specification is always highly relevant to the claim construction analysis. Usually,

it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (internal quotation marks and citations omitted).

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [Which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312–13 (internal quotation marks and citations omitted). "[T]he ordinary meaning of a claim term is its meaning to [an] ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314 (internal citations omitted).

When a court relies solely upon the intrinsic evidence—the patent claims, the specification, and the prosecution history—the court's construction is a determination of law. *See Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). The court may also make factual findings based upon consideration of extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317–19 (internal quotation marks and citations omitted). Extrinsic evidence may assist the court in understanding the underlying technology, the meaning of terms to one skilled in the art, and how the invention works. *Id.* Extrinsic evidence, however, is less reliable and less useful in claim construction than the patent and its prosecution history. *Id.*

"A claim construction is persuasive, not because it follows a certain rule, but because it defines terms in the context of the whole patent." *Renishaw PLC v. Marposs Societa' per*

Azioni, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." *Osram GmbH v. Int'l Trade Comm'n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (internal quotation marks and citation omitted).

The parties agree that the term "effective amount," found in claim 1 of the '527 patent, should be construed as "amount sufficient to produce the desired effect." (D.I. 44 at p. 4). The Court adopts this construction.

The parties dispute the construction of four terms: (1) "dexmedetomidine;" (2) "no more than about 2% decrease in the concentration of dexmedetomidine;" (3) "critically ill;" and (4) "intensive care unit." (*Id.*). The Court addresses each term separately.

1. "dexmedetomidine" (all asserted claims)

   a. *Plaintiff's proposed construction*: "substantially pure, optically active dextrorotary stereoisomer of medetomidine, as the free base or pharmaceutically acceptable salt"

   b. *Defendant's proposed construction*: "substantially pure, optically active dextrorotary stereoisomer of medetomidine, as the free base"

   c. *Court's construction*: "substantially pure, optically active dextrorotary stereoisomer of medetomidine, as the free base or pharmaceutically acceptable salt"

The specification of each of the patents-in-suit sets forth an explicit definition for this term. *See, e.g.*, '158 patent at 3:21-24. That definition aligns with Plaintiff's proposed construction. "When a patentee explicitly defines a claim term in the patent specification, the patentee's definition controls." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1380 (Fed. Cir. 2009). Thus, here, the inventor's lexicography governs. I therefore construe "dexmedetomidine" to mean "substantially pure, optically active dextrorotary stereoisomer of medetomidine, as the free base or pharmaceutically acceptable salt."

2. "no more than about 2% decrease in the concentration of dexmedetomidine" ('106 patent, claim 1)

a. *Plaintiff's proposed construction*: Plain meaning

b. *Defendant's proposed construction*: Indefinite

c. *Court's construction*: Plain meaning

A patent must "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). Defendant's first indefiniteness argument depends on its proposed construction of "dexmedetomidine." Since the Court rejected that construction, this argument is also rejected. Defendant's second argument focuses on the word "about." "When 'about' is used as part of a numeric range, . . . [that use] avoids a strict numerical boundary to the specified parameter [and] [i]ts range must be interpreted in its technologic and stylistic context.'" *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1368 (Fed. Cir. 2008) (quoting *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995)). The '106 patent's specification explains that "'about' . . . as used herein means within an acceptable error range for the particular value as determined by one of ordinary skill in the art." '106 patent at 5:31-33. The specification further states that this "will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system." *Id.* at 5:33-35. In context, a PHOSITA would understand the scope of the "about" limitation with reasonable certainty. Therefore, Defendant's indefiniteness argument is rejected. The term is afforded its plain and ordinary meaning.

3. "critically ill" ('527 patent, claim 10)

a. *Plaintiff's proposed construction*: Plain meaning

b. *Defendant's proposed construction*: Indefinite

c. *Court's construction*: Plain meaning

"'[A] patentee need not define his invention with mathematical precision in order to comply with the definiteness requirement.'" *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (quoting *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 424 F.3d 1374, 1384 (Fed. Cir. 2005)). The term "critically ill" has a recognizable meaning to those having skill in the art. Further, the '527 patent provides examples of medical conditions that may satisfy the "critically ill" limitation. '527 patent at 10:62-11:1. Therefore, Defendant's indefiniteness argument is rejected. The term is afforded its plain and ordinary meaning.

4. "intensive care unit" ('527 patent, claim 8)

   a. *Plaintiff's proposed construction*: "any setting that provides care to critically ill patients, typically characterized by high nurse-to-patient ratios, continuous medical supervision, and intensive monitoring"

   b. *Defendant's proposed construction*: "any setting that provides intensive care"

   c. *Court's construction*: Either "any setting that provides care to critically ill patients" or "any setting that provides intensive care"

The latter part of Plaintiff's proposed construction—"typically characterized by high nurse-to-patient ratios, continuous medical supervision, and intensive monitoring"—is rejected. This language finds no support in the intrinsic record. I cannot discern any material distinction between "any setting that provides care to critically ill patients" and "any setting that provides intensive care." I therefore decline to construe the term further at this time. The parties are permitted to bring up any additional arguments pertaining to this term at the pretrial conference.

Entered this 25 day of May, 2016.

United States District Judge

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

HOSPIRA, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	**No. 16 C 651**
	)	
FRESENIUS KABI USA, LLC,	)	**Judge Rebecca R. Pallmeyer**
	)	
Defendants.	)	

MEMORANDUM OPINION AND ORDER

Plaintiff Hospira, Inc., a Delaware corporation with its primary place of business in Illinois, manufactures pharmaceuticals and medical supplies. At issue in this case is a chemical compound known as dexmedetomidine, which Hospira sells to health care providers under the brand name Precedex. Between 2012 and 2014, Hospira obtained four patents covering a new product made from dexmedetomidine: U.S. Patent Nos. 8,242,158 (the " '158 Patent"), 8,338,470 (the " '470 Patent"), 8,455,527 (the " '527 Patent"), and 8,648,106 (the " '106 Patent"). (Complaint [1] ("Pl.'s Compl."), 3.)

Defendant Fresenius Kabi USA, LLC, is an American subsidiary of a German pharmaceutical manufacturer which is also registered in Delaware and headquartered in Illinois. On December 4, 2015, Fresenius Kabi notified Hospira that it had filed an abbreviated new drug application ("ANDA") with the FDA, seeking approval to market its own proposed dexmedetomidine products prior to the expiry of Hospira's patents. (Answer to Complaint, Affirmative Defenses, and Counterclaims [10] ("Def.'s Answer"), ¶ 16.) Hospira filed suit a month later, alleging patent infringement. (Pl.'s Compl. 8–9.) Fresenius Kabi has denied the allegations and counterclaimed for a declaration that the four patents at issue are invalid or, alternatively, that Fresenius Kabi's actions will not infringe. (Def.'s Answer 22.)

The parties have presented competing interpretations of two terms common to all four patents-in-suit, and of one term unique to the '527 Patent. The court's construction of those terms follows.

BACKGROUND

A. The Patented Invention

Dexmedetomidine is a chemical compound known as an alpha$_2$-adrenergic agonist. (‘158 Patent, JA-2, col. 1 ll. 21–24.) In layman’s terms, this means it stimulates certain receptors in the central nervous system to produce a desired effect. U.S. National Library of Medicine, *Adrenergic Agonists*, Medicinal Subject Headings 2018 (last visited Nov. 27, 2017), https://meshb-prev.nlm.nih.gov/record/ui?ui=D000322. Dexmedetomidine is used primarily as a sedative, though it is also used to treat pain, anxiety, and high blood pressure. (‘158 Patent, JA-2, col. 1 ll. 21–24.) The compound was originally isolated and patented in 1990 by a Finnish corporation, which later licensed the sales rights to Hospira’s predecessor organization, Abbott Laboratories. (Fresenius Kabi USA, LLC’s Opening Claim Construction Brief [43] (“Def.’s Opening Br.”), 2, 4.) Plaintiff Hospira has sold dexmedetomidine-based medications under the Precedex trade name since 1999. (Hospira’s Responsive Claim Construction Brief [47] (“Pl.’s Resp. Br.”), 1.)

The original Precedex product, known as Precedex Concentrate, is sold in 2-mL glass vials containing a concentration of 100 micrograms per milliliter (µg/mL) of dexmedetomidine. (*Id.*) This concentration is too strong to administer directly to patients. Accordingly, hospital personnel are required to dilute Precedex Concentrate with a 0.9% sodium chloride solution to a reach a concentration of just 4 µg/mL before injecting patients with the medication. (*Id.* at 2; JA-260 (“Precedex Concentrate Label”).) In addition, once diluted, the prepared dexmedetomidine solution must be used within 24 hours for maximum potency. (*Id.*)

As Hospira notes, this extra dilution step has obvious drawbacks, including inconvenience, added cost, and increased safety concerns resulting from possible contamination or overdose. (*Id.*) To address these concerns, Hospira developed a new, pre-diluted dexmedetomidine formulation, which it calls Precedex Premix. (*Id.* at 3.) It is for this invention that Hospira filed for and obtained the patents at issue in this case.

Hospira summarized its invention as "premixed pharmaceutical compositions of dexmedetomidine, or a pharmaceutically acceptable salt thereof, that are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration." ('158 Patent, JA-2, col. 1 ll. 61–65.) While surmounting the shortcomings of its original, concentrated formulation, Hospira faced several challenges in developing Precedex Premix: namely, the need to ensure that the product remained stable and potent over a much longer shelf-life. (Pl.'s Resp. Br. 2–3.) After conducting trials with modified chemical formulas, Hospira identified the packaging as the solution to its problems. (*Id*.) Specifically, Hospira asserts, it "discovered that glass packaging exhibited superior stability relative to other packaging materials" such as plastic infusion bags or pre-filled syringes. (*Id*.; '158 Patent, JA-8, col. 13 ll. 22–67.) Hospira found further that "developing a sealed system" could ensure shelf-life stability and product sterility. (Pl.'s Resp. Br. 3.) On this front, Hospira "tested several closure systems for integrity without success before finding a stopper that was compatible with the glass container[.]" (*Id*.)

The '158, '470, and '106 Patents all cover the same basic subject matter—the medication itself—and share a title: "Dexmedetomidine Premix Formulation." (*See*, *e.g.,* '158 Patent, JA-1.) The final, '527 Patent addresses "Methods of Treatment using a Dexmedetomidine Premix Formulation." ('527 Patent, JA-29.) All the patents share a common specification. The core of the invention, Hospira states, is "a 'ready to use' dexmedetomidine formulation in a 'sealed glass container.'" (Pl.'s Resp. Br. 3.)

B. The Disputed Claim Terms

The parties contest three claim terms: "ready to use," "sealed glass container," and "intensive care unit." The first two of these terms are present in every asserted claim throughout all four patents, while the third relates to just one claim in the '527 Patent.

The '158 Patent is representative of the manner in which the terms "ready to use" and "sealed glass container" are used in all four patents.[1] It claims:

> 1. A **ready to use** liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 µg/mL disposed within a **sealed glass container**.
> 2. The **ready to use** liquid pharmaceutical composition of claim 1, further comprising sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.
> 3. The **ready to use** liquid pharmaceutical composition of claim 2, wherein the sodium chloride is present at a concentration of about 0.9 weight percent.
> 4. The **ready to use** liquid pharmaceutical composition of claim 1, wherein the composition is formulated as a total volume selected from the group consisting of 20 mL, 50 mL and 100 mL.

('158 Patent, JA-14, col. 26 ll. 4–18) (emphasis added).

The '527 Method Patent contains 15 claims covering various concentrations, delivery methods, and settings in which the premixed dexmedetomidine formulation may be administered. ('527 Patent, JA-42, col. 25 l. 24–col. 26 l. 31.) Claim 8 contains the disputed term:

> 1. A method of providing sedation to a patient in need thereof, the method comprising administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL, wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient disposed within a sealed glass container.
>
> . . .
>
> 8. The method of claim 1, wherein the composition is administered to the patient in an **intensive care unit**.

[1] The parties agree on this point, and cite to the first-filed '158 Patent in the Joint Appendix when discussing these two terms throughout their briefs. (*See* Def.'s Opening Br. 4 n.3.)

(*Id*. at col. 25 ll. 25–32, col. 26 ll. 16–17) (emphasis added).

C. Prosecution History

The inventors filed the four patent applications between January 4, 2012, and April 22, 2013. ('158 Patent, JA-1; '106 Patent, JA-43.) The Patent Office issued the patents between August 14, 2012, and February 11, 2014, in the order in which they were filed. (*Id*.) The prosecution history of the first-filed '158 Patent reflects the history of the family of patents as a whole.

In the original application, the independent claim of the '158 Patent read:

> 1. A pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 µg/mL, wherein the composition is formulated as a liquid for parenteral administration to a subject, and wherein the composition is disposed with a sealed container as a premixture.

(JA-175.) The phrase "ready to use" and word "glass" to describe the sealed container were not yet present. The Patent Office rejected all four claims as anticipated or made obvious by the prior art: in this case, the label that appears on the Precedex Concentrate product. (*Id*. at 286.) The examiner's comments explained that the Precedex Concentrate label "teaches that the dexmedetomidine HCL formulation must be diluted in 0.9% sodium chloride solution prior to administration" and "provides instructions for dilution." (*Id*.) (emphasis in original). Notably, the label disclosed that Precedex Concentrate was sold in "clear glass vials and . . . ampules." (*Id*. at 261.) The examiner further stated in regards to the claimed "sealed container" that, given the choice between diluting the solution in a sealed versus unsealed container, "[t]he artisan would clearly immediately envisage the mixing of the formulation in a sealed container in order to maintain the sterility of the composition for parenteral administration." (*Id*. at 287.)

In response, the inventors amended the claim to read "wherein the composition is disposed within a sealed glass container as a ready to use premixture." (JA-298) (emphasis in original). In support of these amendments, the record states:

> [Hospira] noted that the claims are directed to a composition comprising 4 µg/mL dexmedetomidine that is a premixture, which does not require dilution prior to administration to a subject. The claimed composition differs from the formulation described by the cited reference, which requires dilution to a concentration of 4 µg/mL dexmedetomidine prior to administration to a patient. As such, [Hospira] maintained that unlike the claimed composition, the formulation disclosed by the cited reference is not a ready to use premixture.

(*Id*. at 299.) As for the modification of "sealed container" to "sealed glass container," Hospira successfully argued that the prior art did not meet the legal standard for inherent anticipation because the examiner's conclusion was based on the "mere probability that the skilled artisan would prepare the dilution in a sealed glass container and not in an unsealed container" made of another substance. (*Id*. at 301–02.) Anticipation "may not be established by probabilities or possibilities," (*Id*. at 301 (citing *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)), and Hospira distinguished Precedex Premix as being "*necessarily* disposed with a sealed glass container." (*Id*. at 302) (emphasis in original).

Hospira further argued that a "sealed glass container" was not obvious in the light of the prior art because a skilled artisan would likely prepare a solution for intravenous delivery to a patient in a plastic infusion bag rather than a sealed glass container. (*Id*. at 303.) While Precedex Concentrate was sold in glass vials, it was not diluted in those same containers. Hospira also presented evidence that distributing Precedex Premix in sealed glass containers exhibited superior potency over a longer shelf life than alternative vessels. (*Id*.) The PTO accepted these arguments as "effective to overcome the previous rejection" for inherent anticipation and obviousness. (JA-421.)

The '158 Patent reached its final form on March 30, 2012, through an amendment requested by the examiner and authorized by the inventors. (*Id*. at 420.) The amendment maintained the inventors' addition of "ready to use" and "glass" to the claims, but rearranged the sentence for grammar and syntax to read:

> 1. A **ready to use** liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 µg/mL disposed within a **sealed glass container**.

(*Id.*; '158 Patent, JA-14, col. 26 ll. 4–8.) The remaining patents underwent a similar process of rejection and modification before being approved by the PTO. (*See, e.g.*, JA-757–66; JA-843–65) (discussing the term "sealed glass container" in the context of the '470 Patent).

DISCUSSION

A. Legal Standards Governing Claim Construction

The claims of a patent define the scope of the invention to which the patentee may exercise his right of exclusivity. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). Where a claim's meaning is disputed, the court must determine its proper construction as a matter of law. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996). Claim construction is an objective exercise, and courts should generally give claim terms the ordinary and customary meaning they would have "to a person of ordinary skill in the art at the time of the invention." *Phillips*, 415 F.3d at 1313. Claim construction often "involves little more than the application of the widely accepted meaning of commonly understood words." *Id*. at 1314 ("In such circumstances, general purpose dictionaries may be helpful."). Importantly, however, judges must always read claims "in the context of the entire patent." *Id*. at 1313.

The Federal Circuit instructed in *Phillips* that if the meaning of a disputed claim term is not readily apparent, the court should first turn to sources of evidence intrinsic to the patent. 415 F.3d at 1314–19. Foremost among these intrinsic sources is the patent's specification, which must include a "full, clear, concise, and exact" description of the claimed invention as the inventor saw it. *Id*. at 1316 (quoting 35 U.S.C. § 112). If the specification defines or gives consistent meaning to certain terms, "the inventor's lexicography governs." *Id*. The same rule applies if an inventor explicitly limits the scope of a term in the specification. *Id*. If the specification merely provides examples or preferred embodiments of an invention, however, *Phillips* warns courts not to confine the patent's claims to those embodiments. *Id*. at 1323; *see also Absolute Software, Inc. v. Stealth Signal, Inc.*, 659 F.3d 1121, 1136 (Fed. Cir. 2011) (declining to limit a claim "where the references to a certain limitation as being the 'invention' are

not uniform, or where other portions of the intrinsic evidence do not support applying the limitation to the entire patent.").

In addition to the specification, the court may look to the patent's prosecution history as further evidence of how the inventor and the Patent Office understood the invention. *Id*. at 1317. The court must be mindful, however, that the prosecution history represents an ongoing discussion, and may be less clear than the specification "and thus less useful for claim construction purposes." *Id*. Finally, while consulting the intrinsic evidence will resolve ambiguities in most situations, courts must sometimes go beyond the contents of the patent itself and consider extrinsic evidence—such as technical dictionaries, treatises, or expert testimony—to aid in claim construction. *Id*. Though the Federal Circuit in *Phillips* outlined several reasons why extrinsic evidence is less reliable than intrinsic evidence, it declined to exclude such evidence provided it is not used to contradict claim language made clear by intrinsic evidence. *Id*. at 1318–19, 1324; *see also Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

With these standards of construction in mind, the court turns to the disputed claim language.

B. "ready to use" (all asserted claims)

Claim Term	**Plaintiff Hospira's Proposed Construction**	**Defendant Fresenius Kabi's Proposed Construction**
"ready to use"	"formulated to be suitable for administration to a patient upon manufacture without dilution or reconstitution"	"suitable for administration to a patient without requiring dilution"

The '158 Patent defines the term "ready to use" as an embodiment of the invention "formulated as 'ready to use' compositions which refer to premixed compositions that are suitable for administration to a patient without dilution." ('158 Patent, JA-3, col. 3 ll. 57–59.) The specification previously defines a "premix" or "premixture" as "a pharmaceutical formulation that does not require reconstitution or dilution prior to administration to a patient." (*Id*. at ll. 48–

50.) Such compositions, the specification continues, do not require dilution by "a clinician, hospital personnel, caretaker, patient, or any other individual." (*Id*. at ll. 53–55.) Here, the inventor has clearly acted as his own lexicographer. *See Philips*, 415 F.3d at 1316. As such, Hospira's proposed construction more accurately describes the scope of the term "ready to use."

Fresenius Kabi contends that its proposed construction appropriately describes the "distinguishing characteristic" of "ready to use"—namely, "the ability to administer the compositions without further dilution." (Def.'s Opening Br. 13.) That construction, however, relies on an incomplete quotation of the patent's definition and cuts out the phrases "formulated and "premixed compositions." Viewing the term "ready to use" in the light of the patent's complete definition confirms that the term should be read as "ready to use" in its original formula or design, not merely "ready to use" whenever no further dilution step is required. *See also Formula, Formulate*, MERRIAM-WEBSTER COLLEGIATE DICTIONARY (10th ed. 1997). Fresenius Kabi contends that relying on the term "premixed" to define "ready to use" is improper; as the terms are not used interchangeably, Fresenius Kabi insists they must mean different things. (Fresenius Kabi USA, LLC's Reply Claim Construction Brief [60] ("Def.'s Reply Br."), 5–6) (citing *Nystrom v. TREX Co.*, 424 F.3d 1136, 1143 (Fed. Cir. 2005)). But "ready to use" compositions can fairly be understood to be a subset of "premixed" compositions—which the specification clearly states are "formulations" that do not require dilution by anyone, at any time. ('158 Patent, JA-3, col. 3 ll. 49–55.) A "ready to use" composition must thus also be "premixed" and incorporate any additional meaning the parent term bears.

The most straightforward reading of the term necessarily implies that the composition is "ready to use" from the moment it leaves Hospira's possession. Fresenius Kabi contends this is an improper "attempt to impute a temporal limitation" onto the term. (Def.'s Reply Br. 3.) Assuming such a temporal limitation is appropriate at all, Fresenius Kabi asserts, the temporal limitation on "ready to use" more appropriately dates to the moment the dexmedetomidine is

removed from the sealed glass container, not to "the specific point of manufacture." (*Id*. at 4.) Thus, "the focus is not on whether the composition had ever been diluted, but whether it requires a dilution step before administration." (Def.'s Opening Br. 13.) The court disagrees. The Defendant's definition is overbroad, and would cover any dexmedetomidine formulation that had been diluted at any point in the past. (Pl.'s Resp. Br. 7.) The specification does not support such a reading.

Fresenius Kabi cites to the prosecution history to bolster its reading, highlighting passages where Hospira distinguished the Precedex Concentrate prior art as "[u]nlike the claimed composition that is formulated at a concentration which is *ready for administration to a patient upon removal from the sealed glass container*." (Def.'s Opening Br. 13) (quoting JA-97–98) (emphasis in original). In this passage again, however, Fresenius Kabi's proposed construction ignores all language stressing that the medication is "formulated" as such. Throughout the patents-in-suit, the inventors stress that the core distinction between Precedex Concentrate and Precedex Premix is that the formulas are different. Any person of ordinary skill in the art ("POSITA") would have to incorporate that distinction in understanding the patents' scope.

Fresenius Kabi also asserts that Hospira is impermissibly trying to "convert its composition claims into product-by-process or method claims." (Def.'s Reply Br. 2) (citing *Vanguard Prods. Corp. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372 (Fed. Cir. 2001)). As Fresenius Kabi reads Hospira's proposed claim construction, Hospira is attempting to redefine its claims to cover "how a composition is made" rather than "what the composition is." (*Id*.) Again, the court disagrees: recognizing the necessary temporal limitations that define the claimed product is not the same as imposing process restrictions on the claims. Fresenius Kabi's position suggests that any "do-it-yourself" product can be transformed into a "ready to use" product after the customer has put it together on his own. This is an untenable conclusion. If a consumer buys a flat-pack bookcase at IKEA, it will never be a "pre-built" bookcase. Some

assembly—even if not done by the consumer himself—will always be required. A bookcase, like a premixed dexmedetomidine formulation, is either "ready to use" from the outset, or not at all. Any POSITA handling a product described as "ready to use" would recognize that it requires no further manipulation by anyone. Fresenius Kabi itself recognized as much when it stated "[t]he appropriate question for infringement is whether the accused infringer sells a product that does not require further dilution." (Def.'s Reply Br. 4.)

Hospira is correct that "ready to use" includes a temporal component, but this court nevertheless declines to adopt Hospira's construction wholesale. The record bears no support for Hospira's attempt to insert the term "upon manufacture." The specification's summary section states that "[t]he present invention relates to premixed pharmaceutical compositions of dexmedetomidine, or a pharmaceutically acceptable salt thereof, that are formulated for administration to a patient, without the need to reconstitute or dilute." ('158 Patent, JA-2, col. 1 ll. 61–64.) As stated above, the definitions section describes "ready to use" compositions in the same manner: calling them "formulations" and "premixed compositions" may imply that the compositions are ready for use "upon manufacture," but such a phrase is not part of the claim. (*Id*. at col. 3 ll. 57–59.)

Indeed, the parties' efforts to draw a line between the moment of manufacture and the moment of dispensing may well be academic: if the glass container is "sealed," the contents of that container are likely "ready to use" when the seal is placed during manufacturing. The patents-in-suit do not anticipate any additional intermediate steps between making and bottling the premixed dexmedetomidine. In most cases, therefore, the parties' constructions overlap. To the extent Defendant suggests that the dexmedetomidine composition may be diluted by anyone else at some point before administration, the court rejects that construction. Likewise, pinpointing the precise moment of readiness to be "upon manufacturing" is unnecessary and overly specific. That is simply not what the claims refer to.

Accordingly, this court adopts the following construction: "formulated to be suitable for administration to a patient without dilution or reconstitution."

C. "sealed glass container" (all asserted claims)

Claim Term	Plaintiff Hospira's Proposed Construction	Defendant Fresenius Kabi's Proposed Construction
"sealed glass container"	"glass container closed to maintain the sterility by having a seal or another closure that passes closure integrity testing"	"closed tightly to prevent unwanted materials entering or exiting the glass container"

The parties do not dispute the meanings of "glass" or "container." Instead, they propose different interpretations of what it means for a glass container to be "sealed." Notably, the specification does not define the term "sealed glass container." The only detailed reference to the subject matter states:

> In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention is disposed in a container or vessel that can maintain the sterility of, or prevent the contamination of, a premixed dexmedetomidine composition that is purified or substantially free of any contaminants. In certain non-limiting embodiments, the container or vessel is a sealed container or vessel.

('158 Patent, JA-6, col. 9 ll. 1–7.) In addition, the specification details at length the process by which Hospira developed the "sealed glass container" by experimenting with different container types and closures.

Hospira seeks to supplant the common-place meaning of "sealed" with a lengthy set of standards referencing the need to maintain sterility and pass FDA-recommended closure-integrity tests. (Pl.'s Resp. Br. 8–9.) This level of detail is unnecessary. For one, whether a container is "sterile" is a separate question from whether it is "sealed." It is just as possible for a sealed container to be keeping contaminants in rather than out. The specification clarifies that a sterile container and a sealed container are not used interchangeably. (*See* '158 Patent, JA-6, col. 9 ll. 1–7) (describing a sterile container and a sealed container as separate non-limiting embodiments of the invention). Furthermore, maintaining sterility is not the only purpose of

sealing the container—Example 6 describes additional aims of potency and stability. ('158 Patent, JA-12, col. 21 ll. 18–44.) The specification does not suggest that one of these goals must be elevated to define the term "sealed" while the others should not. Finally, inserting the phrase "to maintain the sterility"—or any other language suggesting the purpose of the seal—would be redundant. The act of sealing a container already implies that the contents will remain untouched until the seal is broken. The additional language Hospira proposes adds nothing to a POSITA's ability to understand the commonplace word "sealed."

The latter half of Hospira's proposed construction, "by having a seal or another closure that passes closure integrity testing," is similarly unsupported by the specification. Hospira criticizes Fresenius Kabi's construction as "raising more questions than it answers," but in advocating for this court to incorporate the entire body of FDA closure integrity standards by reference, Hospira is guilty of the same transgression. (Pl.'s Resp. Br. 9.) As noted by Fresenius Kabi: "[a]dding all the extra terminology that Hospira asks to add would mean not only collecting material wholesale from third party extrinsic sources, but then would require another round of claim construction briefing to understand what that new terminology would actually require." (Def.'s Reply Br. 7.) While Hospira may prefer the incorporation of its preferred embodiment—a glass container sealed using a "Helvoet FM 259/0 OmniflexPlus fluoropolymer coated stopper"—the specification cannot be read to mean that such a stopper is the only means of sealing the glass container. (*See* '158 Patent, JA-12, col. 21 ll. 1–2.) Nor was that the view of the named inventor or of Hospira's own corporate witness, both of whom confirmed that "a sealed glass container refers to a container that is closed sufficiently [ ] to maintain the integrity of the . . . solution inside the glass bottle." (Dep. of Robert Cedergren, Ex. 1 to Def.'s Reply Br., 194:3–7; Dep. of Rao Tata-Venkata, Ex. 2 to Def.'s Reply Br., 41:9–12.) Hospira's corporate witness, Dr. Rao Tata-Venkata, went further; he pointed out that "'sealed' is a very general term," and observed that, in his experience, "sealed" means "closed with a closure."

(Dep. of Rao Tata-Venkata 41:2–8.) This intrinsic evidence, and the use of the general term "sealed," signals that the patents' claims were intended to sweep broadly.

Fresenius Kabi's proposed construction is closer to the mark, but is arguably too imprecise. This court agrees with Plaintiff Hospira that "sealed" means something beyond "covered" or "closed," and even beyond the Defendant's proposed meaning "closed *tightly*." (Pl.'s Resp. Br. 9) (emphasis added). In common usage, the Defendant's proposal is not incorrect, but in the context of a prescription drug patent a POSITA would read the word "sealed" to suggest something more secure and permanent than just "tightly closed." Thus, in a patent infringement case from the District of Delaware regarding an anti-tumor medication, the court addressed the term "sealed container" and concluded that "[t]he ordinary meaning of the term 'sealed' is different from, and encompasses something more than, the ordinary meaning of the term 'closed.'" *Pharmacia & Upjohn Co. v. Sicor & Sicor Pharm., Inc.*, 447 F. Supp. 2d 363, 373 (D. Del. 2006)

A standard dictionary definition of a "seal" is "a tight and perfect closure (as against the passage of gas or water)." *Seal*, MERRIAM-WEBSTER COLLEGIATE DICTIONARY (10th ed. 1997). The verb "to seal" means either "to fasten with or as if with a seal to prevent tampering," or "to close or make secure against access, leakage, or passage by a fastening or coating." *Id*. Despite Hospira's assertions that a "sealed" container requires rigorous closure testing, the concept is not a complicated one. The court concludes no construction of this term is required. That said, the court does not understand the term "sealed" as broad enough to include containers that are merely "closed" as a person might close a desk drawer or a book. If the court were to adopt a construction of the term, it would adopt Fresenius Kabi's proposal, as it more accurately reflects the broad scope of the chosen claim language.

D. "intensive care unit" ('527 Patent, claim 8)

Claim Term	Plaintiff Hospira's Proposed Construction	Defendant Fresenius Kabi's Proposed Construction
"intensive care unit"	"any setting that provides care to critically ill patients, typically characterized by high nurse-to-patient ratios, continuous supervision, and intensive monitoring"	"any setting that provides care to critically ill patients" OR "any setting that provides intensive care"

Defendant Fresenius Kabi's proposed construction relies of this term relies on the recent findings of Delaware District Court Judge Andrews in a parallel case, *Hospira Inc. v. Amneal Pharm. LLC*, No. 15-cv-697-RGA, 2016 WL 3021719 (D. Del. May 25, 2016). That case featured the same plaintiff seeking to enforce the same four patents at issue in this case. *Id*. at *1. Hospira pushed for the same construction of "intensive care unit" there as here: "any setting that provides care to critically ill patients, typically characterized by high nurse-to-patient ratios, continuous supervision, and intensive monitoring." Judge Andrews declined to adopt Hospira's construction, stating:

> The latter part of Plaintiff's proposed construction—"typically characterized by high nurse-to-patient ratios, continuous medical supervision, and intensive monitoring"—is rejected. This language finds no support in the intrinsic record. I cannot discern any material distinction between "any setting that provides care to critically ill patients" and "any setting that provides intensive care." I therefore decline to construe the term further at this time.

Id. at *3.

Fresenius Kabi urges this court to defer to Judge Andrews' findings. (Def.'s Opening Br. 18–19.) The doctrine of issue preclusion likely does not apply in this situation as the parallel litigation has not reached a final judgment on the merits. *Kollmorgen Corp. v. Yaskawa Elec. Corp.*, 147 F. Supp. 2d 464, 469 (W.D. Vir. 2001) ("[J]udicial statements regarding the scope of patent claims are entitled to collateral estoppel effect in a subsequent infringement suit only to the extent that determination of scope was essential to a final judgment on the question of validity or infringement.") (quoting *A.B. Dick v. Burroughs Corp.*, 713 F.2d 700, 704 (Fed. Cir. 1983)); *but see TM Patents, L.P. v. IBM Corp.*, 72 F. Supp. 2d 370, 379 (S.D.N.Y. 1999)

(holding that a prior construction opinion was a sufficiently final judgment to warrant issue preclusion even where the proceedings never reached a final judgment on the merits). Nevertheless, courts "would be remiss to overlook another district court's construction of the same claim terms in the same patent" given the importance of uniform treatment of patents. *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1329 (Fed. Cir. 2008) (citing *Markman*, 517 U.S. at 390).

This court finds Judge Andrews' reasoning persuasive and would reach the same conclusion even without his guidance, as there appears to be no support in the intrinsic record for the additional elements Hospira requests. In fact, the specification of the '527 Patent militates against Hospira's proposal. The only reference to "intensive care unit" in the '527 Patent states that the term "as used herein refers to any setting that provides intensive care, as described, for example, in U.S. Pat. No. 6,716,867." ('527 Patent, JA-34, col. 10 ll. 33–35.) The patent referenced, No. 6,716,867, is the method of administration patent for the original concentrated dexmedetomidine formulation and analogous to the present '527 Patent. ('867 Patent, Ex. G to Def.'s Opening Br. [43-2].) The text of the '867 Patent, though cross-referenced in the '527 Patent, adds nothing to that definition—the '867 Patent simply repeating that "an intensive care unit includes any setting that provides intensive care." (*Id*. at col. 1 ll. 18–19.) The specification is clear. Intensive care units, in the context of the patents-in-suit, refer to *any setting* where such care is provided, not merely those additionally "characterized by high nurse-to-patient ratios, continuous supervision, and intensive monitoring."

Hospira's proposed construction generates additional confusion. Hospira has not explained what nurse-to-patient ratios qualify as "high" or what "intensive" monitoring entails. These sorts of threshold judgments are not necessary as no POSITA would think the term requires that level of detailed inquiry. True, most intensive care units are likely to reflect the criteria Hospira recites, but even the medical dictionaries cited by Hospira identify these as typical *features* of intensive care units, not limitations. (*See* Pl.'s Resp. Br. 12.) There is no

evidence in the intrinsic record to suggest that nurse-to-patient ratios, continuous supervision, and intensive monitoring should be considered.

The term "intensive care unit" is largely self-explanatory. At the most basic level, it is merely whatever location a given hospital designates as the "intensive care unit." The specification asserts, and the parties agree in their proposed construction, however, that the term as used in the patent goes further: to any setting, regardless of title, where intensive care is provided. As the parties also recognize, "intensive care" involves patients who are seriously or "critically" ill. *See also Intensive Care*, MERRIAM-WEBSTER COLLEGIATE DICTIONARY (10th ed. 1997). Accordingly, the court adopts the Defendant's construction of "intensive care unit" as meaning either "any setting that provides care to critically ill patients" or "any setting that provides intensive care."

CONCLUSION

The claim terms in the '158 Patent, '470 Patent, '527 Patent, and '106 Patent are construed as follows:

Claim Term	**Construction**
"ready to use"	formulated to be suitable for administration to a patient without dilution or reconstitution
"sealed glass container"	no construction required
"intensive care unit"	any setting that provides care to critically ill patients OR any setting that provides intensive care

ENTER:

Dated: November 27, 2017

REBECCA R. PALLMEYER
United States District Judge

US008455527B1

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

(10) **Patent No.: US 8,455,527 B1**
(45) **Date of Patent: *Jun. 4, 2013**

(54) **METHODS OF TREATMENT USING A DEXMEDETOMIDINE PREMIX FORMULATION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/678,148**

(22) Filed: **Nov. 15, 2012**

Related U.S. Application Data

(63) Continuation of application No. 13/541,524, filed on Jul. 3, 2012, now Pat. No. 8,338,470, which is a continuation of application No. 13/343,672, filed on Jan. 4, 2012, now Pat. No. 8,242,158.

(51) **Int. Cl.**
A61K 31/164 (2006.01)

(52) **U.S. Cl.**
USPC **514/396**; 514/816

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

The presently disclosed subject matter relates to pharmaceutical compositions comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the composition is formulated as a liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed container as a premixture. The pharmaceutical compositions can be used, for example, in perioperative care of a patient or for sedation.

15 Claims, No Drawings

METHODS OF TREATMENT USING A DEXMEDETOMIDINE PREMIX FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

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

1. FIELD OF THE INVENTION

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

2. BACKGROUND OF THE INVENTION

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

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

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

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

3. SUMMARY OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4. DETAILED DESCRIPTION

The present invention is based in part on the discovery that dexmedetomidine prepared in a premixed formulation that

does not require reconstitution or dilution prior to administration to a patient, remains stable and active after prolonged storage. Such premixed formulations therefore avoid the cost, inconvenience, and risk of contamination or overdose that can be associated with reconstituting or diluting a concentrated dexmedetomidine formulation prior to administration to a patient.

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

(4.1) Definitions;

(4.2) Pharmaceutical formulations; and

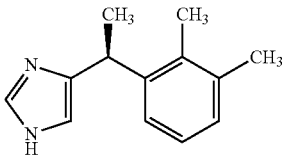
(4.3) Methods of using premixed dexmedetomidine compositions.

4.1 Definitions

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

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

Formula I



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

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

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

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

The term "purified" as used herein refers to material that has been isolated under conditions that reduce or eliminate the presence of unrelated materials, i.e., contaminants, including native materials from which the material is obtained. As used herein, the term "substantially free" is used operationally, in the context of analytical testing of the material. Preferably, purified material substantially free of contaminants is at least 95% pure; more preferably, at least 97% pure, and more preferably still at least 99% pure. Purity can be evaluated, for example, by chromatography or any other methods known in the art. In a specific embodiment, purified means that the level of contaminants is below a level acceptable to regulatory authorities for safe administration to a human or non-human animal.

The term "pharmaceutically acceptable," when used in connection with the pharmaceutical compositions of the invention, refers to molecular entities and compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a human. Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, dispersing agent or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils. For example, water, aqueous solutions, saline solutions, aqueous dextrose or glycerol solutions can be employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in, for example, "Remington's Pharmaceutical Sciences" by Philip P. Gerbino, 21st Edition (or previous editions).

The term "pharmaceutical composition" as used in accordance with the present invention relates to compositions that can be formulated in any conventional manner using one or more pharmaceutically acceptable carriers or excipients. A "pharmaceutically acceptable" carrier or excipient, as used herein, means approved by a regulatory agency of the Federal or a state government, or as listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in mammals, and more particularly in humans.

The term "dosage" is intended to encompass a formulation expressed in terms of μg/kg/day, μg/kg/hr, mg/kg/day or mg/kg/hr. The dosage is the amount of an ingredient administered in accordance with a particular dosage regimen. A "dose" is an amount of an agent administered to a mammal in a unit volume or mass, e.g., an absolute unit dose expressed in mg or μg of the agent. The dose depends on the concentration of the agent in the formulation, e.g., in moles per liter (M), mass per volume (m/v), or mass per mass (m/m). The two terms are closely related, as a particular dosage results from

the regimen of administration of a dose or doses of the formulation. The particular meaning in any case will be apparent from context.

The terms "therapeutically effective dose," "effective amount," and "therapeutically effective amount" refer to an amount sufficient to produce the desired effect.

In some non-limiting embodiments, a "therapeutically effective dose" means an amount sufficient to reduce by at least about 15%, preferably by at least 50%, more preferably by at least 90%, and most preferably prevent, a clinically significant deficit in the activity, function and response of the host. Alternatively, a therapeutically effective amount is sufficient to cause an improvement in a clinically significant condition in the host. These parameters will depend on the severity of the condition being treated, other actions, such as diet modification, that are implemented, the weight, age, and sex of the subject, and other criteria, which can be readily determined according to standard good medical practice by those of skill in the art.

In other non-limiting embodiments a therapeutic response may be any response that a user (e.g., a clinician) will recognize as an effective response to the therapy. Thus, a therapeutic response will generally be an induction of a desired effect, such as, for example, sedation or analgesia.

The term "about" or "approximately" as used herein means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 3 or more than 3 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, preferably up to 10%, more preferably up to 5%, and more preferably still up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value.

4.2 Pharmaceutical Compositions

The compounds and compositions of the invention may be formulated as pharmaceutical compositions by admixture with a pharmaceutically acceptable carrier or excipient. In certain non-limiting embodiments, the compounds or compositions are provided in a therapeutically effective amount to an animal, such as a mammal, preferably a human, in need of treatment therewith for inducing a sedative, anxiolytic, analgesic, or anesthetic effect.

In certain non-limiting embodiments, dexmedetomidine is formulated as a composition, wherein the dexmedetomidine is the only therapeutically active ingredient present in the composition. In another non-limiting embodiments, dexmedetomidine is formulated as a composition, wherein the dexmedetomidine is formulated in combination with at least one or more other therapeutically active ingredient. The formulation is preferably suitable for parenteral administration, including, but not limited to, intravenous, subcutaneous, intramuscular and intraperitoneal administration; however, formulations suitable for other routes of administration such as oral, intranasal, mucosal or transdermal are also contemplated.

The pharmaceutical formulations suitable for injectable use, such as, for example, intravenous, subcutaneous, intramuscular and intraperitoneal administration, include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the form can be sterile and can be fluid to the extent that easy syringability exists. It can be stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, saline, ethanol, polyol (for example, glycerol, propylene glycol, and polyethylene glycol, and the like), suitable mixtures thereof, and oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, benzyl alcohol, sorbic acid, and the like.

In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monosterate and gelatin. Sterile injectable solutions may be prepared by incorporating the dexmedetomidine in the required amounts in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter or terminal sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

Preferably the formulation may contain an excipient. Pharmaceutically acceptable excipients which may be included in the formulation are buffers such as citrate buffer, phosphate buffer, acetate buffer, and bicarbonate buffer; amino acids; urea; alcohols; ascorbic acid; phospholipids; proteins, such as serum albumin, collagen, and gelatin; salts such as EDTA or EGTA, and sodium chloride; liposomes; polyvinylpyrollidone; sugars, such as dextran, mannitol, sorbitol, and glycerol; propylene glycol and polyethylene glycol (e.g., PEG-4000, PEG-6000); glycerol; glycine; lipids; preservatives; suspending agents; stabilizers; and dyes. As used herein, the term "stabilizer" refers to a compound optionally used in the pharmaceutical compositions of the present invention in order to avoid the need for sulphite salts and increase storage life. Non-limiting examples of stabilizers include antioxidants. Buffer systems for use with the formulations include citrate; acetate; bicarbonate; and phosphate buffers.

The formulation also may contain a non-ionic detergent. Preferred non-ionic detergents include Polysorbate 20, Polysorbate 80, Triton X-100, Triton X-114, Nonidet P-40, Octyl α-glucoside, Octyl β-glucoside, Brij 35, Pluronic, and Tween 20.

The parenteral formulations of the present invention can be sterilized. Non-limiting examples of sterilization techniques include filtration through a bacterial-retaining filter, terminal sterilization, incorporation of sterilizing agents, irradiation, and heating.

The route of administration may be oral or parenteral, including intravenous, subcutaneous, intra-arterial, intraperitoneal, ophthalmic, intramuscular, buccal, rectal, vaginal, intraorbital, intracerebral, intradermal, intracranial, intraspinal, intraventricular, intrathecal, intracisternal, intracapsular, intrapulmonary, intranasal, transmucosal, transdermal, or via inhalation.

Administration of the above-described parenteral formulations may be by periodic injections of a bolus of the preparation, or may be administered by intravenous or intraperitoneal administration from a reservoir which is external (e.g., an intravenous bag) or internal (e.g., a bioerodible implant, a bioartificial or organ). See, e.g., U.S. Pat. Nos. 4,407,957 and 5,798,113, each incorporated herein by reference in their entireties. Intrapulmonary delivery methods and apparatus are described, for example, in U.S. Pat. Nos. 5,654,007, 5,780,014, and 5,814,607, each incorporated herein by reference in their entireties. Other useful parenteral delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, pump delivery, encapsulated cell delivery, liposomal delivery, needle-delivered injection, needle-less injection, nebulizer, aeorosolizer, electroporation, and transdermal patch. Needle-less injector devices are described in U.S. Pat. Nos. 5,879,327; 5,520,639; 5,846,233 and 5,704,911, the specifications of which are herein incorporated herein by reference in their entireties. Any of the formulations described herein can be administered in these methods.

In yet another non-limiting embodiment, the therapeutic compound can be delivered in a controlled or sustained release system. For example, a compound or composition may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump may be used (see Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:201; Buchwald et al., 1980, Surgery 88:507; Saudek et al., 1989, N. Engl. J. Med. 321:574). In another embodiment, polymeric materials can be used (see Langer and Wise eds., 1974, Medical Applications of Controlled Release, CRC Press: Boca Raton, Fla.; Smolen and Ball eds., 1984, Controlled Drug Bioavailability, Drug Product Design and Performance, Wiley, N.Y.; Ranger and Peppas, 1983, J. Macromol. Sci. Rev. Macromol. Chem., 23:61; Levy et al., 1985, Science 228:190; During et al., 1989, Arm. Neurol., 25:351; Howard et al., 9189, J. Neurosurg. 71:105). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, 1984, in Medical Applications of Controlled Release, Vol. 2, pp. 115-138).

In certain non-limiting embodiments, the premixed dexmedetomidine composition comprises dexmedetomidine, or a pharmaceutically acceptable salt thereof, at a concentration of between about 0.005 μg/mL and about 100 μg/mL, or between about 0.005 μg/mL and about 50 μg/mL, or between about 0.005 μg/mL and about 25 μg/mL, or between about 0.005 μg/mL and about 15 μg/mL, or between about 0.005 μg/mL and about 10 μg/mL, or between about 0.005 μg/mL and about 7 μg/mL, or between about 0.005 μg/mL and about 5 μg/mL, or between about 0.005 μg/mL and about 4 μg/mL, or between about 0.005 μg/mL and about 3 μg/mL, or between about 0.005 μg/mL and about 2 μg/mL, or between about 0.005 μg/mL and about 1 μg/mL, or between about 0.005 μg/mL and about 0.5 μg/mL, or between about 0.005 μg/mL and about 0.05 μg/mL.

In certain non-limiting embodiments, the premixed dexmedetomidine composition comprises dexmedetomidine, or a pharmaceutically acceptable salt thereof, at a concentration of between about 3.5 μg/mL and about 4.5 μg/mL, or between about 3 μg/mL and about 5 μg/mL, or between about 2.5 μg/mL and about 5.5 μg/mL, or between about 2 μg/mL and about 6 μg/mL, or between about 1.5 μg/mL and about 6.5 μg/mL, or between about 1 μg/mL and about 7 μg/mL, or between about 0.5 μg/mL and about 10 μg/mL.

In certain non-limiting embodiments, the premixed dexmedetomidine composition comprises dexmedetomidine at a concentration of about 0.5 μg/mL, or about 1 μg/mL, or about 1.5 μg/mL, or about 2 μg/mL, or about 2.5 μg/mL, or about 3 μg/mL, or about 3.5 μg/mL, or about 4 μg/mL, or about 4.5 μg/mL, or about 5 μg/mL, or about 5.5 μg/mL, or about 6 μg/mL, or about 6.5 μg/mL, or about 7 μg/mL, or about 7.5 μg/mL, or about 8 μg/mL, or about 8.5 μg/mL, or about 9 μg/mL, or about 9.5 μg/mL, or about 10 μg/mL, or about 10.5 μg/mL, or about 11 μg/mL, or about 11.5 μg/mL, or about 12 μg/mL, or about 12.5 μg/mL, or about 13 μg/mL, or about 13.5 μg/mL, or about 14 μg/mL, or about 14.5 μg/mL, or about 15 μg/mL, or about 15.5 μg/mL, or about 16 μg/mL, or about 16.5 μg/mL, or about 17 μg/mL, or about 17.5 μg/mL, or about 18 μg/mL, or about 18.5 μg/mL or about 19 μg/mL, or about 19.5 μg/mL, or about 20 μg/mL.

In certain non-limiting embodiments, the premixed dexmedetomidine composition comprises dexmedetomidine at a concentration of about 4 μg/mL.

In certain non-limiting embodiments, the premixed dexmedetomidine composition is formulated as a liquid.

In certain non-limiting embodiments, the premixed dexmedetomidine composition is formulated at a pH of between about 1 and about 10, or between about 1 and about 8, or between about 1 and about 6, or between about 1 and about 4, or between about 1 and about 2. In other non-limiting embodiments, the premixed dexmedetomidine composition is formulated at a pH of between about 2 and about 10, or between about 4 and about 8, or between about 4 and about 7. In other non-limiting embodiments, the premixed dexmedetomidine composition is formulated at a pH of between about 4.7 and about 6.2. In a preferred non-limiting embodiment, the premixed dexmedetomidine composition is formulated at a pH of between about 4.5 and about 7.0.

In other non-limiting embodiments, the premixed dexmedetomidine composition comprises dexmedetomidine mixed or dissolved in a sodium chloride saline solution. The saline solution can comprise sodium chloride present at a concentration of between about 0.05 weight percent and about 10 weight percent, or between about 0.05 weight percent and about 5 weight percent, or between about 0.05 weight percent and about 3 weight percent, or between about 0.05 weight percent and about 2 weight percent, or between about 0.05 weight percent and about 1 weight percent. In one preferred, non-limiting embodiment, the sodium chloride is present at a concentration of about 0.9 weight percent.

In certain embodiments, the weight percent of the saline solution is a percent weight/weight of the premix composition. In certain embodiments, the weight percent of the saline solution is a percent weight/volume of the premix composition.

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

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

In one non-limiting example, the 0.9% NaCl solution is formulated by mixing 9.0 g NaCl/1000 mL of water. In certain embodiments, the premix compositions of the present invention are formulated by adding 0.118 g dexmedetomidine HCl plus 9.0 g NaCl into the same 1000 mL of water. The

solution can then be mixed with addition 0.9% NaCl solution to achieve a desired concentration of dexmedetomidine, for example, 4 μg/mL.

In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention is disposed in a container or vessel that can maintain the sterility of, or prevent the contamination of, a premixed dexmedetomidine composition that is purified or substantially free of any contaminants. In certain non-limiting embodiments, the container or vessel is a sealed container or vessel.

In certain non-limiting embodiments, the dexmedetomidine composition of the present invention is disposed in a container or vessel and is formulated as a premixture.

In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention is disposed in a container or vessel and is formulated as a single use dosage. In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention is disposed in a container or vessel and is formulated as a dosage for multiple use.

In certain non-limiting embodiments, the container or vessel includes, but is not limited to, glass vials (for example, but not limited to, flint glass vials), ampoules, plastic flexible containers, for example, but not limited to, PVC (polyvinyl chloride) containers, VisIV™ plastic containers (Hospira, Inc., Lake Forest, Ill.), and CR3 elastomer copolyester ether containers (Hospira, Inc., Lake Forest, Ill.), CZ resin containers, poly propylene containers and syringes.

In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention can be stored as a liquid in an aliquot having a total volume of between about 1 and 500 mL, or between about 1 and 250 mL, or between about 1 and 200 mL, or between about 1 and 150 mL, or between about 1 and 125 mL, or between about 1 and 120 mL, or between about 1 and 110 mL, or between about 1 and 100 mL, or between about 1 and 90 mL, or between about 1 and 80 mL, or between about 1 and 70 mL, or between about 1 and 60 mL, or between about 1 and 50 mL, or between about 1 and 40 mL, or between about 1 and 30 mL, or between about 1 and 20 mL, or between about 1 and 10 mL, or between about 1 and 5 mL.

In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention can be stored as a liquid in an aliquot having a total volume of about 5 mL, or about 10 mL, or about 15 mL, or about 20 mL, or about 25 mL, or about 30 mL, or about 35 mL, or about 40 mL, or about 45 mL, or about 50 mL, or about 55 mL, or about 60 mL, or about 65 mL, or about 70 mL, or about 75 mL, or about 80 mL, or about 85 mL, or about 90 mL, or about 95 mL, or about 100 mL, or about 105 mL, or about 110 mL, or about 115 mL, or about 120 mL, or about 125 mL, or about 130 mL, or about 135 mL, or about 140 mL, or about 145 mL, or about 150 mL, or about 200 mL, or about 250 mL, or about 500 mL.

In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention can be stored as a liquid in an aliquot having a total volume of about 20 mL.

In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention can be stored as a liquid in an aliquot having a total volume of about 50 mL.

In certain non-limiting embodiments, the premixed dexmedetomidine composition of the present invention can be stored as a liquid in an aliquot having a total volume of about 100 mL.

4.3 Methods of Using Premixed Dexmedetomidine Compositions

In accordance with the invention, there are provided methods of using a premixed dexmedetomidine composition. In certain non-limiting embodiments, the present invention provides for preoperative treatment of a patient to reduce the response of the autonomic nervous system to stimuli during an operation by administering a dexmedetomidine composition of the invention, as described in U.S. Pat. No. 5,344,840. In other non-limiting embodiments, the dexmedetomidine compositions of the present invention can be administered as a sedative. In certain embodiments, the composition is administered preoperatively to potentiate the effect of an anesthetic, wherein administration of the composition reduces the amount of anesthetic required to achieve a desired level of anesthesia. In certain embodiments, the dexmedetomidine compositions of the present invention can be administered as an anxiolytic analgesic premedication prior to the operation with or without administration of an amount of an anesthetic effective to achieve a desired level of local or general anesthesia. In certain embodiments, the dexmedetomidine compositions of the present invention are formulated as a pharmaceutical composition for use in a method of sedation, analgesia or treatment of anxiety or hypertension.

In certain non-limiting embodiments, the patient treated with the premixed dexmedetomidine composition of the invention is intubated. The patient may be intubated prior to, during, or after administration of the premixed dexmedetomidine composition. The patient may be intubated by the nasotracheal, endotracheal, direct oral laryngoscopy or by fibreoptic routes, or via tracheotomy, for example, while being treated in an intensive care unit (ICU), which, as used herein refers to any setting that provides intensive care, as described, for example, in U.S. Pat. No. 6,716,867. For example, the compositions of the invention can be used for sedating a patient in an intensive care unit which means rendering a patient calm and treating conditions that affect patient comfort, such as pain and anxiety, in any setting that provides intensive care.

In other non-limiting embodiments, the premixed dexmedetomidine compositions of the present invention can be administered to a patient as a perioperative treatment. In certain embodiments, the composition can be administered as a premedication prior to an operation. In certain embodiments, the premixed dexmedetomidine compositions of the present invention can be used in the manufacture of a medicament for perioperative treatment of mammals to reduce the responses of the autonomic nervous system to stressful stimuli during an operation, for example, as described in U.S. Pat. No. 5,344,840.

In other non-limiting embodiments, the premixed dexmedetomidine compositions of the present invention can be administered to a patient as an adjunct anesthesia. For example, the composition can be administered with or without an amount of an anesthetic effective to achieve a desired level of local or general anesthesia, for example, as described in U.S. Pat. No. 5,344,840. In certain embodiments, administration of the compositions of the present invention reduces the amount of anesthetic required to achieve a desired level of anesthesia.

In other non-limiting embodiments, the patient treated with the premixed dexmedetomidine composition is critically ill. In one embodiment, the patient suffers from one or more medical conditions. In certain embodiments, the medical condition is a lung problem, brain problem, heart problem, liver problem, kidney problem, eye or ear problem, gastrointesti-

nal problem, or skin problem. Non-limiting examples of lung problems include respiratory distress syndrome, pneumonia, bronchopulmonary dysplasia, apnea of prematurity, and pneumothorax. Non-limiting examples of brain problems include intraventricular hemorrhage, and cerebral palsy. Non-limiting examples of liver problems include jaundice. Non-limiting examples of heart problems include patent ductus arteriosus. Non-limiting examples of eye problems include retinopathy of prematurity, myopia, and strabismus. Non-limiting examples of other medical conditions includes heroin withdrawal, cocaine withdrawal, alcohol fetal syndrome, HIV-positive status, and Tay Sachs disease.

In one embodiment, the patient has undergone surgery. The patient may undergo surgery prior to, during, or after administration of the premixed dexmedetomidine composition. Non-limiting examples of surgery include cardiopulmonary bypass.

In other non-limiting embodiments, the premixed dexmedetomidine compositions of the present invention can be administered to a patient as an anxiolytic or analgesic agent, for example, as described in U.S. Pat. Nos. 5,344,840 and 6,716,867. In one non-limiting example, the method comprises local epidural or intraspinal administration of the premixed dexmedetomidine composition of the invention.

In other non-limiting embodiments, the premixed dexmedetomidine compositions of the present invention can be administered to a patient to lower intraocular pressure, for example, in the treatment of glaucoma, as described in U.S. Pat. No. 5,304,569.

In certain embodiments, the premixed dexmedetomidine compositions of the present invention do not include any other active ingredient, or therapeutic agent, other than dexmedetomidine.

In certain non-limiting embodiments of the present invention, the premixed dexmedetomidine composition can be administered as a single continuous dose over a period of time. For example, the premixed dexmedetomidine composition can be administered intravenously for a period of time of between about 1 and about 10 minutes, or between about 1 and about 20 minutes, or between about 1 and about 30 minutes, or between about 1 and about 2 hours, or between about 1 and about 3 hours, or between about 1 and about 4 hours, or between about 1 and about 5 hours, or between about 1 and about 6 hours, or between about 1 and about 7 hours, or between about 1 and about 8 hours, or between about 1 and about 9 hours, or between about 1 and about 10 hours, or between about 1 and about 11 hours, or between about 1 and about 12 hours, or between about 1 and about 13 hours, or between about 1 and about 14 hours, or between about 1 and about 15 hours, or between about 1 and about 16 hours, or between about 1 and about 17 hours, or between about 1 and about 18 hours, or between about 1 and about 19 hours, or between about 1 and about 20 hours, or between about 1 and about 21 hours, or between about 1 and about 22 hours, or between about 1 and about 23 hours, or between about 1 and about 24 hours, and administered at a dosage of between about 0.005 μg/kg/hr and about 5 μg/kg/hr, or between about 0.005 μg/kg/hr and about 4.5 μg/kg/hr, or between about 0.005 μg/kg/hr and about 3 μg/kg/hr, or between about 0.005 μg/kg/hr and about 2.5 μg/kg/hr, or between about 0.005 μg/kg/hr and about 2 μg/kg/hr, or between about 0.005 μg/kg/hr and about 1.5 μg/kg/hr, or between about 0.005 μg/kg/hr and about 1 μg/kg/hr, or between about 0.005 μg/kg/hr and about 0.5 μg/kg/hr, or between about 0.005 μg/kg/hr and about 0.25 μg/kg/hr.

In other non-limiting embodiments of the present invention, the premixed dexmedetomidine composition can be administered as a loading dose followed by a maintenance dose over a period of time. For example, the loading dose can comprise administration of the premixed dexmedetomidine composition at a first dosage amount for a first period of time, followed by administration of the maintenance dose at a second dosage amount for a second period of time. The loading dose can be administered for a period of time of between about 1 and about 5 minutes, or between about 1 and about 10 minutes, or between about 1 and about 15 minutes, or between about 1 and about 20 minutes, or between about 1 and about 25 minutes, or between about 1 and about 30 minutes, or between about 1 and about 45 minutes, or between about 1 and about 60 minutes. Following the loading dose, the maintenance dose can be administered for a period of time as described above for a single continuous dose.

In certain non-limiting embodiments, the premixed dexmedetomidine composition, when administered as a single continuous, loading or maintenance dose, is administered for a period of time of about 1 hour to about 7 days, or about 1 hour to about 4 days, or about 1 hour to about 48 hours, or about 1 hour to about 36 hours, or about 1 hour to about 24 hours, or about 1 hour to about 12 hours.

In certain non-limiting embodiments, the premixed dexmedetomidine composition, when administered as a single continuous, loading or maintenance dose, is administered for a period of time of about 24 hours to about 120 hours, or about 24 hours to about 108 hours, or about 24 hours to about 96 hours, or about 24 hours to about 72 hours, or about 24 hours to about 48 hours, or about 24 hours to about 36 hours.

When administered as a loading dose followed by a maintenance dose, the loading dose and/or maintenance dose can be a dose of between about 0.005 μg/kg/hr and about 5 μg/kg/hr, or between about 0.005 μg/kg/hr and about 4.5 μg/kg/hr, or between about 0.005 μg/kg/hr and about 3 μg/kg/hr, or between about 0.005 μg/kg/hr and about 2.5 μg/kg/hr, or between about 0.005 μg/kg/hr and about 2 μg/kg/hr, or between about 0.005 μg/kg/hr and about 1.5 μg/kg/hr, or between about 0.005 μg/kg/hr and about 1 μg/kg/hr, or between about 0.005 μg/kg/hr and about 0.5 μg/kg/hr, or between about 0.005 μg/kg/hr and about 0.25 μg/kg/hr.

In a preferred non-limiting embodiment, the premixed dexmedetomidine composition is administered as a loading dose followed by a maintenance dose, wherein the loading dose is about 1 μg/kg/hr for a period of about 10 minutes, followed by a maintenance dose of between about 0.2 μg/kg/hr to about 1 μg/kg/hr, more preferably, between about 0.2 μg/kg/hr to about 0.7 μg/kg/hr.

In other preferred non-limiting embodiments, the premixed dexmedetomidine composition is administered as a loading dose followed by a maintenance dose, wherein the loading dose is about 0.5 μg/kg/hr for a period of about 10 minutes, followed by a maintenance dose of between about 0.2 μg/kg/hr to about 1 μg/kg/hr, more preferably, between about 0.2 μg/kg/hr to about 0.7 μg/kg/hr.

In certain non-limiting embodiments, the dosage of premixed dexmedetomidine composition administered as a single continuous, loading or maintenance dose, is titrated until a desired effect is achieved.

In some patients, the quality of the sedation achieved by administering the premixed dexmedetomidine composition of the present invention can be unique. In one non-limiting example, a patient sedated by the premixed dexmedetomidine composition is arousable and oriented. The patient can be awakened and is able to respond to questions. The patient is aware and can tolerate an endotracheal tube. Should a deeper level of sedation be required or desired, an increase in dose of

the composition of the invention can be administered to transit the patient into a deeper level of sedation.

In certain non-limiting embodiments, the compositions of the invention can be administered to non-ventilated patients who require sedation, anxiolysis, analgesia, or hemodynamic stability in an amount to achieve a sedative, anxiolytic, analgesic or hemodynamic stabilizing effect in the patient.

5. EXAMPLES

The following examples are merely illustrative of the presently disclosed subject matter and they should not be considered as limiting the scope of the invention in any way.

Example 1

Selection of Packaging Components for the Premixed Dexmedetomidine Pharmaceutical Composition

In order to identify suitable primary packaging components for the 4 μg/mL premixed dexmedetomidine composition in 0.9% NaCl, stability studies were conducted in various configurations including glass vials, ampoules, plastic flexible containers (CR3 elastomer copolyester ether containers (Hospira, Inc., Lake Forest, Ill.), PVC and VisIV™ plastic containers (Hospira, Inc., Lake Forest, Ill.)), and Ansyr® syringes (Hospira, Inc., Lake Forest, Ill.). A batch of premixed dexmedetomidine composition was prepared at the premix concentration of 4 μg/mL, in 0.9% NaCl. Solution was filled into 20 mL ampoules, 50 mL glass vials, 100 mL PVC flexible containers, 100 mL CR3 elastomer copolyester ether flexible containers (Hospira, Inc., Lake Forest, Ill.), 50 mL VisIV™ plastic (Hospira, Inc., Lake Forest, Ill.) flexible containers, and 10 mL Ansyr® syringes (Hospira, Inc., Lake Forest, Ill.), and all configurations were autoclaved. The pH and potency (using HPLC method) of the sterilized samples were determined. The stability of the autoclaved samples under accelerated conditions (40° C./75% RH) was also evaluated over a period of 5 months (Table 1).

Potency was evaluated using a HPLC method. Post sterilization potency values ranged from 73-88%. The solution pHs varied from 4.7-6.2 following an in-process result of 6.0. Two weeks samples stored under ambient conditions were tested for pH, potency and related substances. The two weeks potency results were considered as time zero results because the 4 μg/mL formulation remains stable at room temperature for more than 2 weeks. Comparison of potency results at time zero in different configurations indicated a drop in potency of premixed dexmedetomidine composition filled in CR3 elastomer copolyester ether bags (Hospira, Inc., Lake Forest, Ill.) and VisIV™ plastic bags (Hospira, Inc., Lake Forest, Ill.), after sterilization (Table 1).

The stability of the autoclaved samples under accelerated conditions (40° C./75% RH) was also evaluated over a period of 5 months (Table 1). After five months under accelerated conditions the potency of the premixed dexmedetomidine composition in glass ampoules and vials remained at about 98% while that in the syringe was found to be about 90%. In PVC and CR3 elastomer copolyester ether bags (Hospira, Inc., Lake Forest, Ill.), after the initial potency loss no further loss of potency was observed during the five month period.

TABLE 1

4 μg/mL Premixed Dexmedetomidine Composition in Normal Saline Formulation Stability

	2 Week/ 25° C. Avg Potency (%)	pH	1 Month/ 40° C. Avg Potency (%)	pH	2 Month/ 40° C. Avg Potency (%)	3 Month/ 40° C. Avg Potency (%)	5 Month/ 40° C. Avg Potency (%)
Ampoule	99.0	5.0	99.0	5.6	97.7	98.3	98.7
Vial	98.2	6.7	99.4	6.3	98.0	98.3	98.6
Syringe	95.0	5.5	94.6	5.7	92.2	89.5	90.8
CR3	80.2	4.7	79.5	4.8	NT	75.3	79.2
PVC	79.9	4.8	81.4	4.6	NT	79.0	76.7
Vis-IV ™	95.8	5.9	92.8	5.8	NT	94.0	NT

NT—Not tested

The cause of potency loss in PVC bags and CR3 elastomer copolyester ether bags (Hospira, Inc., Lake Forest, Ill.) during autoclaving was investigated. Related substances testing on autoclaved premixed dexmedetomidine composition filled in PVC and CR3 elastomer copolyester ether bags (Hospira, Inc., Lake Forest, Ill.) revealed that potency drop did not occur due to degradation, because the total percent of impurities was much less than 20% (Table 2). Loss of potency may be due to either adsorption (restricted to the surface of the flex bag) and/or absorption (not restricted to the surface) of the drug in to the flex bags. To confirm the absorption/adsorption phenomena, the CR3 elastomer copolyester ether bags (Hospira, Inc., Lake Forest, Ill.) and PVC bags that showed 20% potency loss were emptied and rinsed with McOH. The rinse solvent was tested for dexmedetomidine. Nearly all the drug was recovered from CR3 elastomer copolyester ether bags (Hospira, Inc., Lake Forest, Ill.)—indicating adsorption and only 1% of the drug was recovered from PVC bags—indicating absorption, since drug dissolves in DEHP.

The related substances results indicated that premixed dexmedetomidine composition in VisIV™ plastic bags (Hospira, Inc., Lake Forest, Ill.) had high impurity levels (Table 2), higher than levels observed in ampoules, vials, syringes, PVC bags and CR3 elastomer copolyester ether bags (Hospira, Inc., Lake Forest, Ill.).

TABLE 2

Impurity Results for 4 μg/mL Premixed Dexmedetomidine Composition

	2 week/25° C. Total impurity (%)	1 Month/40° C. Total impurity (%)
Ampoule	0.66%	0.54%
Vial	0.02%	NT
Syringe	0.49%	1.48%
CR3	2.61%	5.88%
PVC	2.26%	NT
VisIV ™	19.08%	7.02%

Example 2

Development in ADDVantage® PVC (Hospira, Inc., Lake Forest, Ill.) Admixture System

In this study three 250 mL ADDVantage® PVC bags (Hospira, Inc., Lake Forest, Ill.) were spiked with 10 mL of dexmedetomidine concentrate (100 μg/mL) to obtain a final concentration of 4 μg/mL. As a control, a glass bottle was spiked in the same manner. Upon thorough mixing of the samples, an

aliquot was withdrawn for subsequent potency analysis. The bag was then allowed to sit on the bench top for various interval testing. The results showed that there is a drop in potency after the initial mixing period and a slight decrease thereafter (Table 3).

TABLE 3

4 μg/mL Premixed Dexmedetomidine Composition ADDVantage ® PVC bag (Hospira, Inc., Lake Forest, IL) Admixture Study

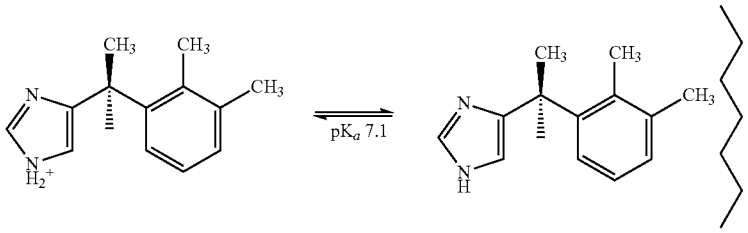
Time Following Admixture	% Loss from Control*
Immediately	5.3
4 Hours	5.6
8 Hours	6.0
24 Hours	5.5
48 Hours	5.8
72 Hours	6.0
7 Days	6.1

*Average of three spiked bags compared to glass bottle.

Example 3

Modification of the Premixed Dexmedetomidine Composition Formulation

The pH of the premixed dexmedetomidine composition formulation can affect the adsorption of dexmedetomidine molecule. The free base form of dexmedetomidine is more adsorptive. At lower pH~4.0, most of the dexmedetomidine is in the ionized form, which minimized adsorption and thereby loss in potency. Buffered formulations were tested to determine whether loss of potency in flex bags can be minimized.



Buffered formulations were prepared at different pHs 3.0, 3.4, 4.0, and 4.5 using acetate, citrate, lactate and ascorbate buffer. Since the pKa for dexmedetomidine is about 7.1, at this pH the molecule might be protonated sufficiently to retard adsorption. Post-autoclave potency values dropped approximately 10% in all instances; this was an improvement from the 20% decrease observed in the unbuffered formulation in Example 1.

In a second study, additives were formulated with the premixed dexmedetomidine composition to prevent adsorption of the dexmedetomidine to CR3 elastomer copolyester ether (Hospira, Inc., Lake Forest, Ill.). The following additives were tested: ethyl alcohol, benzyl alcohol, methyl paraben, propyl paraben, PEG 1000, polysorbate 20 and 80, propylene glycol. Formulations prepared included additives in both buffered and unbuffered premixed dexmedetomidine composition. Both these reformulation strategies reduced potency loss.

Stability testing of the 4 μg/mL premixed dexmedetomidine composition (unbuffered saline formulation), in glass vials and ampoules stored at 25° C., after 9 months was performed. Potency remained relatively unchanged from initial measurements. Additionally, the largest single impurity detected in the samples was present at a concentration of 0.06%.

Example 4

Stability of the Premixed Dexmedetomidine Composition

The stability of dexmedetomidine hydrochloride to acidic, basic, oxidative and photolytic stress was examined. In order to demonstrate the resiliency of dexmedetomidine, even when present in extremely low levels (ppm or μg/mL levels), dilute solutions of dexmedetomidine (approx. 13.3 μg/mL) were separately subjected to acidic, basic, oxidative and photolytic stress and then diluted with 0.9% Sodium Chloride to a final nominal concentration of 4 μg/mL and assayed by HPLC with a photodiode array (PDA) detector for spectral peak purity analysis. Each sample was injected in duplicate. The stress conditions are listed in Table 4.

TABLE 4

Stress Conditions

Stress Condition	Description
Acid	5.0 mL of a 40 μg/mL stock Dexmedetomidine Hydrochloride solution* and 10 mL of 5N Hydrochloric Acid were added to 20 mL scintillation vial. The vial was placed in an oven at 60° C. for 8 hours. The solution was then diluted with 0.9% NaCl to 4 μg/mL.
Base	5.0 mL of a 40 μg/mL stock Dexmedetomidine Hydrochloride solution* and 5 mL of 2N Sodim Hydroxide were added to 20 mL scintillation vial. The vial was placed in an oven at 60° C. for 4 hours. The solution was then diluted with 0.9% NaCl to 4 μg/mL.

TABLE 4-continued

Stress Conditions

Stress Condition	Description
Thermal	5.0 mL of a 40 μg/mL stock Dexmedetomidine Hydrochloride solution* was added to 20 mL scintillation vial. The vial was placed in an oven at 60° C. for 8 hours. The solution was then diluted with 0.9% NaCl to 4 μg/mL.
H_2O_2	5.0 mL of a 40 μg/mL stock Dexmedetomidine Hydrochloride solution* and 5 mL of 0.3% Hydrogen Peroxide were added to 20 mL scintillation vial. The vial was placed in an oven at 60° C. for 8 hours. The solution was then diluted with 0.9% NaCl to 4 μg/mL.
Light	5.0 mL of a 40 μg/mL stock Dexmedetomidine Hydrochloride solution* were added to 20 mL scintillation vial and placed into a photochemical reaction unit for 24 hours. The solution was then diluted with 0.9% NaCl to 4 μg/mL.
Control	5.0 mL of a 40 μg/mL stock Dexmedetomidine Hydrochloride solution* was added to 20 mL scintillation vial. The vial was not subjected to any stress condition. The solution was then diluted with 0.9% NaCl to 4 μg/mL.

*Stock solution of dexmedetomidine HCl was prepared in 0.9% NaCl solution.

The peak purity analysis shows that under all stress conditions the parent peak were spectrally pure, attesting to the assay being performed under conditions of specificity. See Table 5 for Potency Results.

Under oxidative conditions, the sample showed highest amount of degradation (12.7%) compared to the control sample. Appropriate precautions are taken during manufacturing and packaging to prevent oxidative stress.

Thermal stress studies indicate that the premixed dexmedetomidine composition is stable at high temperature. It is also confirmed by accelerated stability studies, wherein potency values remained within shelf life specifications over a period of 6 months. Moreover the premixed dexmedetomidine composition is a terminally sterilized product. Hence, it is expected that premixed dexmedetomidine composition would remain stable if exposed to temperature excursions during transportation or storage.

TABLE 5

Forced Degradation Results

Samples ID	Assay
Control Sample	98.4%
Acid Sample	95.2%
Base Sample	93.8%
Heat Sample	98.4%
Oxidation Sample	85.7%
Light Sample	92.0%

Example 5

Manufacture of the Premixed Dexmedetomidine Composition Formulation

A 4 μg/mL premixed dexmedetomidine composition can be manufactured according to the following process: Water for Injection is added to a mixing tank to approximately 110% of the final volume and heated to 80° C. Nitrogen sparging in the tank is started and maintained throughout the manufacturing process. Water for Injection is then cooled and a sufficient amount of water is withdrawn from the tank to leave approximately 90% of the final volume in the mix tank. Dexmedetomidine HCl is then added to the tank and mixed for not less than 15 minutes. Sodium chloride is then added and mixed. The solution is then divided into batch size. An in-process sample is then evaluated for pH and potency. The nitrogen protection is maintained.

Filtering of Dexmedetomidine Composition

The dexmedetomidine solution is filtered prior to filling in a clinician-useable container. For the 20 mL batches, solution is filtered through Pall Nylon 66, 0.45 μm filter membrane with a pre filter. For 50 and 100 mL batches, solution is filtered through Nylon 66, 0.22 μm filter membrane with a pre filter. A filter compatibility study was performed using Pall Nylon 66 0.45 μm filter. It was determined that filters had little to no impact on the premixed dexmedetomidine composition product after 52 hours of recirculation. The prolonged exposure of these filter materials did not produce any significant potency or pH changes in the drug product (See Table 6). Additionally, there was no change in bubble point for the filters before and after exposure.

TABLE 6

Filter compatibility testing

	Pall Nylon 66 filter (Pall Corp., Port Washington, NY)	
Time Sample Tested	Potency (%)	pH
Pre-filtration Tank (0 hr)	99.8	6.30
5 minute static filter hold sample	97.3	6.01
One hour tank	99.4	6.17
Six hour tank	99.1	6.18
Eight hour tank	99.2	6.23
25 hour tank	98.9	6.24
52 hour tank	99.3	6.17

Nitrogen Protection During Filling

The transfer line from solution manufacturing to filling is optionally flushed with filtered nitrogen gas prior to filling. The filling equipment, including all lines are purged with nitrogen before starting to fill the product. An atmosphere of filtered nitrogen gas is maintained in the headspace of the surge bottle. After filling, the headspace of the container is gassed with nitrogen to achieve not more than 5% of oxygen in the headspace.

Hold Time

The following time limits will be applied to manufacture of the subject drug product:

Total time for filtration and filling: NMT (Not More Than) 16 hours

Total time for manufacturing (from compounding to end of filling): NMT 24 hours

Sterilization

The premixed dexmedetomidine composition is terminally sterilized. Vials filled with the composition are autoclaved using 15-30 minutes exposure at 121-124° C.

Container Closure System

The 4 μg/mL premixed dexmedetomidine composition can be manufactured in three configurations: 20 mL fill in 20 mL vial, 50 mL fill in 50 mL vial and 100 mL fill in 100 mL vial. Examples of packaging components for the 20 mL, 50 mL and 100 mL configurations are listed in Tables 7, 8, and 9 below.

TABLE 7

Container Closure System for 4 μg/mL Premixed Dexmedetomidine Composition, 20 mL Primary Packaging Materials

Kimble USP Type I, Clear Tubing Glass Vial, Sulfur-Treated, 20 mm, 20 mL (Kimble Chase, Vineland, NJ)
West 4432/50 Teflon 2 coated Gray rubber Closure (Stopper), 20 mm (West Pharmaceutical Services, Inc.)
Seal, Flip-Off ® (Blue or Gray) elastomer stoppers, 20 mm (West Pharmaceutical Services, Inc., Lionville, PA)

TABLE 8

Container Closure System for 4 μg/mL Premixed Dexmedetomidine Composition, 50 mL Primary Packaging Materials

Gerresheimer USP Type I, Glass Vial (Bottle), Sulfur-Treated, 28 mm, 50 mL (Gerresheimer Glass Inc., Vineland, NJ)
Helvolet FM 259/0 Gray with OmniflexPlus ® Fluoropolymer coating Rubber Closure (Stopper), 28 mm (Helvoet Pharma, Datwyler USA, Pennsauken, NJ)
Aluminum Seal, Overseal Assembly, 3 piece, 28 mm

TABLE 9

Container Closure System for 4 μg/mL Premixed Dexmedetomidine Composition, 100 mL Primary Packaging Materials
Gerresheimer USP Type I, Glass Bottle, Sulfur-Treated, 100 mL (Gerresheimer Glass Inc., Vineland, NJ)
Helvolet FM 259/0 Gray with OmniflexPlus ® Fluoropolymer coating Rubber Closure (Stopper), 28 mm (Helvoet Pharma, Datwyler USA, Pennsauken, NJ)
Aluminum Seal, Overseal Assembly, 3 piece, 28 mm

Batch Formula

Examples of qualitative and quantitative batch formula for a registration batch and a commercial batch for a 4 μg/mL premixed dexmedetomidine (dexmedetomidine hydrochloride) composition, for a 20, 50, and 100 mL presentation are presented in Tables 10 and 11 below.

TABLE 10

Batch Formula for 4 μg/mL Premixed Dexmedetomidine Hydrochloride Composition, 20 mL

Component	Registration Stability Batch Size:	Maximum Commercial Batch Size:
Dexmedetomidine HCl	2.832 mg	25.96 mg
Sodium Chloride	5.4 g	49.5 g
Water for Injection USP	q.s. to 600 Liters	q.s. to 5500 Liters
Nitrogen NF[3]	A.R.	A.R.

q.s. = Quantity sufficient
A.R. = As required
Factored to 100% basis.
The final pH range of the finished product is 4.5-7.0.

Nitrogen is used to displace air during manufacturing (i.e. to blanket the formulation and to fill the vial headspace).

TABLE 11

Batch Formula for 4 μg/mL Premixed Dexmedetomidine Hydrochloride Composition, 50 & 100 mL

Component	Registration Stability Batch Size:	Maximum Commercial Batch Size:
Dexmedetomidine HCl	4.72 mg	33.04 mg
Sodium Chloride	9 g	63 g
Water for Injection USP	q.s. to 1000 Liters	q.s. to 7000 Liters
Nitrogen NF[3]	A.R.	A.R.

q.s. = Quantity sufficient
A.R. = As required
Factored to 100% basis.
The final pH range of the finished drug product is 4.5-7.0.

Nitrogen is used to displace air during manufacturing (i.e. to blanket the formulation and to fill the vial headspace).

In-Process Specification

Examples of in-process controls during the manufacturing process for the 4 μg/mL premixed dexmedetomidine composition are presented in Table 12.

TABLE 12

In-Process Specification

Unit Operation	In-Process Control/Test	Procedures or Methods	In-Process Limit
Solution Preparation (Compounding)	pH	USP <791>	4.5-7.0
	Assay	HPLC	94-106%

TABLE 12-continued

In-Process Specification

Unit Operation	In-Process Control/Test	Procedures or Methods	In-Process Limit
Filling Process	Weight/volume control	Perform fill weight/volume checks per SOP	Meets requirements

An example of final product limits for physical, chemical, and biological testing of 4 μg/mL premixed dexmedetomidine composition are listed in the Table 13.

TABLE 13

Premixed Dexmedetomidine Composition Specifications

Test	Acceptance Criteria	
Clarity	Solution is clear. Solution does not contain one or more particles visible upon attentive inspection	
Assay	90.0%-110.0% (9.00 mg/mL-1.10 mg/mL)	
Color	Colorless	
pH	4.5-7.0	
Volume	Label Claim	Acceptable Range
	20 mL	20.5-22.5 mL
	50 mL	50.0-54.5 mL
	100 mL	102.0-10.8.0 mL
Optical Purity	NMT 1.0%	
Related Substances:		
A. Individual	A. NMT 0.5%	
B. Total	B. NMT 1.0%	
Sodium Chloride	90.0%-110.0% (8.1 mg/mL-9.9 mg/mL)	
Particulate Matter	NMT 25/mL [3] 10 mm NMT 3/mL [3] 25 mm	
Sterility	Meets USP requirements	
Bacterial Endotoxin	NMT 0.08 EU/mL	

Example 6

Stopper Selection for Glass Vials

The objective was to have three presentations of Precedex® (dexmedetomidine hydrochloride, Hospira, Inc., Lake Forest, Ill.) premix Injection 4 μg/mL: 20 mL, 50 mL and 100 mL. Precedex® concentrate Injection 100 μg/mL is currently marketed in 2 mL glass vial with West 4416 Teflon coated elastomer stopper (West Pharmaceutical Services, Inc., Lionville, Pa.).

Uncoated infusion stoppers, were evaluated. 28 mm Helvoet 5330 rubber stopper (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.), EDPM rubber stoppers (EPSI, Franksville, Wis.) and West 4432 elastomer stoppers (West Pharmaceutical Services, Inc.) were investigated. During feasibility testing loss of potency and stopper extractables were observed. The performance of coated stoppers was compared with that of uncoated stoppers (West 4432 and Helvoet 5330) by conducting feasibility studies on West 4588/40 FluoroTec® elastomer stoppers (West Pharmaceutical Services, Inc., Lionville, Pa.). Results showed a clear benefit to using a coated stopper vs. the uncoated stopper. The potency remained stable with the coated stopper. Hence for Precedex® Injection, it was planned to implement coated stoppers in order to mimic the current product and prevent any drug adsorption.

Helvoet FM 259/0 OmniflexPlus® fluoropolymer coated rubber stoppers (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.) were evaluated. Chemical compatibility testing was favorable; upon autoclave no change in potency or pH was observed and no significant amount of impurities detected. The OmniflexPlus® coated stopper from Helvoet, was examined for determining the self sealing characteristics of the stopper when penetrated multiple times with hypodermic needle. This is a dye ingress test. The new stopper/vial/3-piece overseal combination passed this test. Helvoet OmniflexPlus® coated stopper passed the Rocky Mount pressure test at the required 80 psi criterion. These stoppers, vials and overseals were also evaluated by Tech Ops for functional testing to confirm that the stoppers can be pierced without being pushed into the vial. All testing indicated that the stoppers are acceptable for use.

Feasibility stability studies were conducted by preparing a batch of Precedex® Injection 4 μg/mL and filling into 50 mL vials with the Helvoet OmniflexPlus® stoppers followed by autoclaving. Samples were stored under accelerated (40° C./75% relative humidity, inverted) and long term (25° C./60% relative humidity) conditions. Initial testing showed no loss in potency, no change in pH, and virtually no measurable impurities. The 1 month stability testing of samples stored inverted at 40° C. showed slight drop in potency (2%). This trend in potency drop continued at 2 months under accelerated conditions with further 2% drop in potency. After 3 months under accelerated conditions the potency values remain unchanged as compared to that of 2 months, indicating that potency values have leveled off. Similar trend in drop of potency during the first three months of storage was observed for long term stability conditions (25° C./60% relative humidity) but the percent drop was less. The total percent drop in potency over three months under long term conditions was 1.1%. Stability testing at 4 and 5 months for samples stored under accelerated and long term conditions confirmed that potency values had almost leveled off, with small drop in potency values. During 1 month impurity testing numerous small impurity peaks that totaled over 0.5% of the drug peak were observed. A placebo batch was prepared to confirm whether the peaks are related to the stopper or the drug. Results indicated that impurities were related to the stopper.

Plastic vials were also evaluated for Precedex® premix Injection 4 mcg/mL. Two types of plastic vials were used: CZ resin and poly propylene vials. West 4432 Teflon coated 20 mm elastomer stopper (West Pharmaceutical Services, Inc.) was used for both the plastic vials. The pH, potency and impurities of Precedex® Injection 4 mcg/mL filled in plastic vials and stored under accelerated conditions over a period of 3 months was determined. Similar trend in potency drop was observed. The total % impurities were found to increase over a period of 3 months for both CZ resin vials and polypropylene vials, but the total % of impurities of CZ resin vials was less than that of polypropylene vials. CZ resin vials were found to better as compared to polypropylene vials in terms of drop in potency and total impurities.

Since the drug is present at such a low concentration 4 μg/mL, even ppb levels of impurities would have a significant contribution toward the impurity limit. Moreover the Precedex® related substances method was developed to detect organic impurities at ppb levels. This method requires detection at non-discriminating low wavelength of 210 nm and high injection volume of 500 μl, which render it highly sensitive to detect any organic impurity, including stopper extractables.

Extractables

West 4432/50 Teflon 2 Coated Elastomer Stoppers (West Pharmaceutical Services, Inc.)

The West 4432/50 Teflon 2 coated elastomer stopper, 20 mm is used for Precedex® Injection 4 μg/mL, 20 mL presentation. The stoppers have been qualified for use based on the results of compendial biological, physiochemical and other characterization tests. The related substance testing of Precedex® Injection has not shown any unidentified peaks that exceed the specification of NMT 0.2%, suggesting that extractables are not an issue for Precedex® Injection in this container closure system.

Helvoet FM 259/0 Omniflex® Fluoropolymer Coated Rubber Stoppers (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.)

The Helvoet Omniflex® fluoropolymer coated FM259/0 gray bromobutyl 28 mm rubber stoppers (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.) (ready-to-use) are used for Precedex® Injection 4 μg/mL, 50 and 100 mL presentations. The stoppers have been qualified for use based on the results of compendial biological, physiochemical and other characterization tests performed

During related substances analysis of the exhibit batches of Precedex® 4 μg/mL Injection, unidentified impurity peaks were observed in chromatograms of 50 and 100 mL presentation samples. During investigation of the source of chemical constituents responsible for the 'unidentified impurity peaks', it was found that these peaks also appeared in chromatograms of 0.9% NaCl placebo formulation filled into 50 mL vials with Helvoet FM259/0 rubber stoppers (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.), but were absent in those of 0.9% NaCl placebo formulation filled into glass ampoules. Additionally identical peaks were observed in chromatograms of Helvoet FM259/O rubber stopper (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.) extract solution analyzed by Precedex® related substances method. The extract was prepared by autoclaving (121° C. for 60 minutes) 30 stoppers in 300 mL purified water, yielding an extract of 2 cm^2 stopper surface area per mL water. The results from these investigative studies confirmed that 'unidentified impurity peaks' observed at specific relative retention times were not dexmedetomidine HCl related, but were extractables from Helvoet rubber stoppers used in the container/closure system. It was expected that stopper extractables would be detected at such low limits of detection, i.e. ppb levels, as a highly sensitive LC-UV 210 nm related substances method was used for a highly potent very low concentration (4 μg/mL) product.

The chemical constituents responsible for peaks in specific relative retention times were determined to be extractables from 28 mm Helvoet FM259/O rubber stoppers (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.), part of container closure system for Precedex® Injection 50 and 100 mL. Moreover no peaks were found in these specific relative retention times in chromatograms of forced degradation samples of dexmedetomidine HCl or Precedex® Injection filled in ampoules. Hence in the calculation of single largest related substance and total related substances, peaks in relative retention time ranges: 0.71-0.80, 1.10-1.30, 1.50-1.80 are excluded.

In an effort to quantify the highest levels of observed individual extractable and total extractable, dexmedetomidine HCl was used as a surrogate standard for all stopper extractables. Since, the Helvoet FM259/O rubber stopper (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.) extractables responsible for the peaks in Precedex® related substances profile could not be identified. Through 6 months stability testing the highest % of extractables was observed in Prece-

dex® stability samples stored at 30° C./65% relative humidity for 3 months. The largest individual extractable % peak area was found to be 0.95% or 38 ppb and total extractable % peak area, calculated by adding the % peak areas of all the peaks in the RRT of 0.71-0.80, 1.10-1.30, 1.55-1.80, was found to be 2.7% or 108 ppb.

Helvoet FM259/O rubber stoppers (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.) passed the 'Elastomeric Closures for Injections' testing. As per Helvoet technical documentation the total amount of extractables was determine to be 0.8 mg/100 mL or 8 ppm for a total surface area of 100 cm^2. The surface area of a 28 mm Helvoet stopper is approximately 6.45 cm^2, the total acceptable amount of extractable for each 28 mm Helvoet FM259/O rubber stopper (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.) on an average would be 0.05 mg/100 mL or 500 ppb. Additionally as per USP the total organic content of purified water should not exceed 0.5 mg/L or 500 ppb. The highest levels of observed extractables in Precedex® Injection are at least 5 times lower than the acceptable levels of extractable in purified water and acceptable levels of extractable in the qualified Helvoet stoppers.

USP 'In vitro cytotoxicity test' and USP 'Intracutaneous test and systemic injection test' were performed on Helvoet stopper extracts. The results show that stoppers meet the requirements of these tests, confirming the safety of the stoppers and any stopper related extractables. The 'In vitro cytotoxicity test' was repeated for Helvoet 28 mm stoppers that were used in the exhibit batch to demonstrate the safety of the stoppers. The stopper extract was prepared by autoclaving the stoppers at 121° C. for 1 hour in 0.9% NaCl yielding an extract of 2 cm^2 stopper surface area per mL water. This extraction condition closely mimics Precedex® Injection manufacturing conditions and also meets the extraction requirements of USP 'In vitro cytotoxicity test' testing. Precedex® injection is formulated in 0.9% NaCl and the final product i.e. Precedex® Injection in container-closure is autoclaved at 121° C. for 20-40 minutes. Additionally while investigating the source of 'unidentified impurity peaks' Helvoet FM259/O rubber stopper (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.) aqueous extracts were prepared by autoclaving the stoppers at 121° C. for one hour and then tested by the Precedex® related substances method. The results demonstrated that the chemical constituents responsible for the peaks were also present in the Helvoet FM259/O rubber stopper (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.) aqueous extracts. The stoppers passed the USP 87 testing indicating that the stopper extractables are non cytotoxic.

According to Helvoet Pharma, Helvoet FM259/O Omniflex® fluoropolymer coated rubber stoppers (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.) have been used for other marketed products, and there have been no reported cases of toxicity issues arising due to stopper extractables.

Identification of Extractables

Diligent efforts were made to characterize and identify the extractables. Helvoet's extractables report lists a number of potential extractable compounds. From Helvoet's list, the most likely to be responsible for the peaks observed in the Precedex® chromatograms were selected:

BHT
Irganox-1076
Irganox-1010
Stearic Acid
Palmitic Acid
Sulphur

Samples of these compounds were obtained, and solutions were prepared and injected into an HPLC using the Precedex® related substances method. None of these compounds matched the relative retention time of the stopper extractable peaks in Precedex® sample chromatograms. In general, the substances listed above are all too hydrophobic (retained too long on the C18 column with the isocratic mobile phase that is used for the method, 40% aqueous phosphate buffer pH 7.0/60% methanol).

Since these peaks were also observed in the chromatograms of Helvoet FM259/O rubber stopper (Helvoet Pharma, Datwyler USA, Pennsauken, N.J.) extract solution, a concentrated stopper extract solution was prepared by first by autoclaving a large number of stoppers in purified water, and then concentrating the extract by liquid-liquid extraction into dichloromethane and then rotovaping and re-suspending the residue into a small volume of methanol/water. LC-UV analysis of this concentrated stopper extract show the same peaks of interest as observed in Precedex® chromatogram, but at much higher levels (approx 100 times larger peak size). This concentrated extract solution was then analyzed by LC-MS using the Waters Q-TOF instrument with the electrospray source in positive ion mode and observed at least one of the peaks of interest in the mass spec TIC chromatogram; the mass spectrum of the peak has been obtained and appears to have what might be the molecular ion peak at m/z 158; exact mass analysis of this peak and its pattern of isotope peaks predicts some empirical formulas. Compounds with these empirical formula and known usage in the rubber industry were tested but without success.

Solvent extracts of the stoppers were prepared and analyzed by gas chromatography-mass spectrometry. Analysis revealed the presence of two low molecular weight rubber oligomers previously reported by Helvoet. These oligomers are not commercially available for identification confirmation; however, their hydrophobic character makes it unlikely that they would elute near dexmedetomidine in the related substances HPLC method.

A pure extractable sample was isolated by combining multiple fractions collected from repeated HPLC separations of a stopper extract. Attempts to obtain an EI+ mass spectrum by direct probe mass spectrometry and gas chromatography-mass spectrometry were unsuccessful, suggesting that the stopper extractable is nonvolatile and possibly thermally labile.

The pure extractable sample was analyzed by IR and elemental analysis. Both of these techniques suggested that the extractable contains only carbon, oxygen and hydrogen. No indication of nitrogen, sulfur or any other heteroatom was observed.

The chemical additives that perform variety of functions, including plasticizers, fillers, etc are the most significant source of chemical entities observed as extractables. There are several reasons which makes identifying the extractables challenging and at times impossible. Each functional additive category contains representatives from several molecular structures. For example, consider the category of antidegradants, subcategory antioxidants, which includes aromatic amines, sterically hindered phenols, phosphites, phosphonites, and thioethers. To further complicate the picture, chemical additives are often not pure compounds but mixtures of related structures. For examples "Abietic Acid" which is an organic chemical filler used in certain types of rubber, in reality is a complex mixture of chemical entities, all of which could appear as extractables/leachables. Chemical additives can also react and degrade within the rubber/polymer matrix during or subsequent to compounding process. As an example of this consider, the trivalent phosphorus, or phosphate antioxidant, a common tradename for which is Irgafos

168. This compound reacts with and thereby destroys oxidizing agents, such as hydroperoxides, to form the corresponding pentavalent phosphorus species, or phosphate.

In addition to the foregoing, the following must also be considered when analyzing extractables/leachables:

Monomers and high molecular weight oligomers derived from incomplete polymerization reactions.

Surface residues, such as heavy oils and degreasing agents on the surface of metal canisters and containers.

Chemical additives on the surfaces of container closure component fabrication machinery, such as mould release agents, antistatic and antislip agents, etc.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

Patents, patent applications, publications, product descriptions, and protocols are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

What is claimed is:

1. A method of providing sedation to a patient in need thereof, the method comprising administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient disposed within a sealed glass container.

2. The method of claim **1**, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 μg/mL.

3. The method of claim **1**, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 μg/mL.

4. The method of claim **1**, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 μg/mL.

5. The method of claim **1**, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 μg/mL.

6. The method of claim **1**, wherein the composition is administered perioperatively.

7. The method of claim **6**, wherein the composition is administered before or after surgery.

8. The method of claim **1**, wherein the composition is administered to the patient in an intensive care unit.

9. The method of claim **1**, wherein the patient is non-ventilated or intubated.

10. The method of claim **1**, wherein the patient is critically ill.

11. The method of claim **1**, wherein the composition is administered by an intravenous infusion.

12. The method of claim **1**, wherein the composition is administered as an anxiolytic.

13. The method of claim **1**, wherein the composition is administered as an adjunct to an anesthetic.

14. The method of claim **1**, wherein the composition is administered as an analgesic.

15. The method of claim **1**, wherein the composition is administered as an anti-hypertensive agent.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

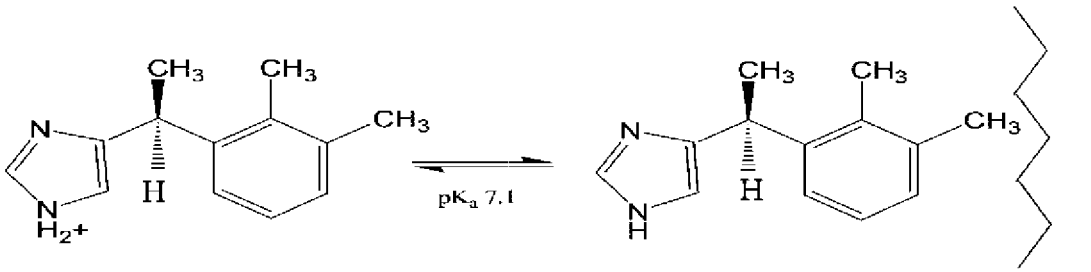
PATENT NO. : 8,455,527 B1
APPLICATION NO. : 13/678148
DATED : June 4, 2013
INVENTOR(S) : Priyanka Roychowdhury and Robert A. Cedergren

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

At Column 15, Lines 27-44, please replace the paragraph and the chemical formula with the following paragraph and formula:

--The pH of the premixed dexmedetomidine composition formulation can affect the adsorption of dexmedetomidine molecule. The free base form of dexmedetomidine is more adsorptive. At lower pH ~ 4.0, most of the dexmedetomidine is in the ionized form, which minimized adsorption and thereby loss in potency. Buffered formulations were tested to determine whether loss of potency in flex bags can be minimized.



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Signed and Sealed this
Fourteenth Day of February, 2017

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)
U.S. Pat. No. 8,455,527 B1

Column 20, Lines 15-38, please delete Table 13 and replace with the following Table 13:

Table 13 Premixed Dexmedetomidine Composition Specifications

Test	Acceptance Criteria
Clarity	Solution is clear. Solution does not contain one or more particles visible upon attentive inspection
Assay	90.0% - 110.0% (9.00 mg/mL – 11.10 mg/mL)
Color	Colorless
pH	4.5 – 7.0
Volume	Label Claim / Acceptable Range 20 mL / 20.5 – 22.5 mL 50 mL / 50.0 – 54.5 mL 100 mL / 102.0 – 108.0 mL
Optical Purity	NMT 1.0%
Related Substances A. Individual B. Total	 A. NMT 0.5% B. NMT 1.0%
Sodium Chloride	90.0% - 110.0% (8.1 mg/mL – 9.9 mg/mL)
Particulate Matter	NMT 25/mL ≥ 10 mm NMT 3/mL ≥ 25 mm
Sterility	Meets USP requirements
Bacterial Endotoxin	NMT 0.08 EU/mL

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HOSPIRA, INC. and ORION CORPORATION, Plaintiffs, v. EUROHEALTH INTERNATIONAL SARL and WEST-WARD PHARMACEUTICAL CORP., Defendants.	C.A. No. 14-487-GMS
HOSPIRA, INC. and ORION CORPORATION, Plaintiffs, v. EUROHEALTH INTERNATIONAL SARL and WEST-WARD PHARMACEUTICAL CORP., Defendants.	C.A. No. 14-1008-GMS

SECOND AMENDED JOINT CLAIM CONSTRUCTION CHART

Pursuant to Paragraph 3 of the Scheduling Order (D.I. 31), Plaintiffs Hospira, Inc. and Orion Corporation and Defendants Eurohealth International SARL and West-Ward Pharmaceutical Corp., hereby submit this Amended Joint Claim Construction Chart, attached hereto as Exhibit A, in preparation for the claim construction hearing scheduled in this matter. The parties certify that in accordance with the Scheduling Order they met and conferred on July 20, 2015 and thereafter in order to narrow the number of claim construction issues in this matter.

This Chart addresses the claim construction positions of the parties regarding U.S. Patent No. 6,716,867 ("the '867 patent") and the parties agree that any terms in the asserted claims of the '867 patent not appearing in Exhibit A do not require construction by the Court. The parties reserve their right to update and/or supplement their proposed claim constructions with the *Markman* briefing in this case.

Respectfully submitted,

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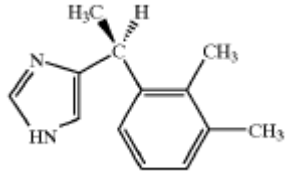
EXHIBIT A

Joint Claim Construction Chart for U.S. Patent No. 6,716,867 ("the '867 patent")

Hospira, Inc. et al. v. Eurohealth Int'l SRL et al.,

Civil Action Nos. 14-487, 14-1008 (GMS)

Claim	Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
1-2, 4-12	"effective amount"	Agreed upon construction: "an amount sufficient to produce the desired effect"	
1-12	"patient"	Agreed upon construction: "human or animal patient"	
1-12	"remains"	Agreed upon construction: "continues to be"	
1-12	"intensive care unit"	Agreed upon construction: "any setting that provides care to critically ill patients, typically characterized by high nurse-to-patient ratios, continuous medical supervision, and intensive monitoring"	
1-12	"sedating a patient in an intensive care unit"	Agreed upon construction: "rendering a patient calm and managing patient comfort in any setting that provides care to critically ill patients, typically characterized by high nurse-to-patient ratios, continuous medical supervision, and intensive monitoring"	
1-12	"arousable and orientated"	Agreed upon construction: "capable of being awakened, aware of one's environment, and able to interact with others"	
1-12	"dexmedetomidine"	"substantially pure, optically active dextrorotary stereoisomer of medetomidine, as the free base or pharmaceutically acceptable salt" **Intrinsic Evidence**	"substantially pure, optically active dextrorotary stereoisomer of medetomidine, as the free base" **Intrinsic Evidence** '867 Patent: *See, e.g.*, col. 1, ll. 12-14, ("The present invention relates to

		'867 Patent Specification *See, e.g.,* '867 patent at 2:66-3:8; 3:19-20; 5:31-40; 5:53-55; 7:4-6; 7:62-64 **Prosecution History of the '867 Patent** *See, e.g.,* Amendment dated August 9, 2002 (JNT-PRECEDEX00371768); Amendment and Request for Continued Examination dated May 2, 2003 (JNT-PRECEDEX00371797).	the use of dexmedetomidine or a pharmaceutically acceptable salt thereof in intensive care unit (ICU) sedation."); col. 1, ll. 19-22, ("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."); col. 5, ll. 5-7 ("Dexmedetomidine or a pharmaceutically acceptable salt thereof can be administered perorally, transmucosally, transdermally, intravenously or intramuscularly."); col. 5, ll. 31-32 ("The chemical form for dexmedetomidine can be the free base or an acid addition salt"); claims 1-5 ("dexmedetomidine or a pharmaceutically acceptable salt thereof"); *see also* col. 2, l. 66 to col. 3, l.10 ("Dexmedetomidine, or (+)-(S)-4-[1-(2,3-dimethylphenyl) ethyl]-1H-imidaZole, has the following formula:  "); col. 3, ll. 19-23, ("Medetomidine, which is the

			racemic mixture of dexmedetomidine and levomedetomidine, is known as a selective and potent α2-agonist and has been described in US. Pat. No. 4,544,664 as an antihypertensive agent and in US. Pat. No. 4,670,455 as a veterinary sedative-analgesic agent.") col. 14, ll. 13-50, (Claims 1 through 12)
6-12	"loading dose"	"a dose that may be given at the onset of therapy with the aim of achieving the target concentration rapidly and that is distinct from, and comparatively larger than, its associated maintenance dose" **Intrinsic Evidence** **'867 Patent Specification** *See, e.g.*, '867 patent at 5:5-31; 5:53-6:5; 6:61-7:9; 7:57-8:7; 8:59-62; 9:5-9; 9:23-26; 9:50-54; 10:6-11; 10:41-43; 11:20-22; 11:48-51; 12:23-25; 13:2-4; *see generally* Examples 1-3 (5:45-13:52).	"dose administered to achieve a target concentration" **Intrinsic Evidence** '867 Patent: *See, e.g*, claims 8-12 (claiming overlapping ranges for loading and maintenance dose); *see also* col. 5, ll. 14-30 ("The dose range of dexmedetomidine can be described as target plasma concentrations. The plasma concentration range anticipated to provide sedation in the patient population in the ICU varies between 0.1-2 ng/ml depending on the desired level of sedation and the general condition of the patient. These plasma concentrations can be achieved by intravenous administration by using a bolus dose and continuing it by a steady maintenance infusion. For example, the dose range for the bolus to achieve the forementioned plasma concentration range in a human is about 0.2-2 ug/kg . . . to be administered in about 10 minutes or slower,

			followed by a maintenance dose of about 0.1-2.0 ug/kg/h . . . . "); *see generally* Examples 1-3 (5:45-13:52), including: Example 3, at col. 11, ll. 6-10 ("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."); *c.f.* *id.* at col. 9, ll. 38-40 ("A dexmnedetomidine[*sic*] infusion (0.5 to 0.7 µg/kg/h) was started when the patient arrived in the ICU") (no mention of loading dose as distinct from maintenance dose); *id.* at col. 12, ll. 11-13 ("The dexmedetomidine infusion was maintained between 0.3 and 0.7 µg/kg/h and no additional sedatives were required.") (no mention of distinct loading dose).
6-12	"maintenance dose"	"a dose given as a continuous infusion that may be titrated in order to maintain the desired effect" **Intrinsic Evidence** *See, e.g.*, '867 patent at 5:5-31; 5:53-6:5; 6:61-7:9; 7:57-8:7; 8:59-62; 9:5-9; 9:23-26; 9:50-54; 10:6-11; 10:41-43; 11:20-22; 11:48-51; 12:23-25; 13:2-4; *see generally*	"dose administered to maintain a target concentration or desired effect" **Intrinsic Evidence** '867 Patent: *See, e.g,* claims 8-12 (claiming overlapping ranges for loading and maintenance dose); *see also*

		Examples 1-3 (5:45-13:52).	col. 5, ll. 5-7 ("Dexmedetomidine or a pharmaceutically acceptable salt thereof can be administered perorally, transmucosally, transdermally, intravenously or intramuscularly.") id. at col. 5, ll. 14-30 ("The dose range of dexmedetomidine can be described as target plasma concentrations. The plasma concentration range anticipated to provide sedation in the patient population in the ICU varies between 0.1-2 ng/ml depending on the desired level of sedation and the general condition of the patient. These plasma concentrations can be achieved by intravenous administration by using a bolus dose and continuing it by a steady maintenance infusion. For example, the dose range for the bolus to achieve the forementioned plasma concentration range in a human is about 0.2-2 ug/kg . . . to be administered in about 10 minutes or slower, followed by a maintenance dose of about 0.1-2.0 ug/kg/h . . . . "); *see generally* Examples 1-3 (5:45-13:52), including: Example 1 col. 5, l. 67 – col. 6, l. 5 ("After the clinical effects of sedation became evident (approximately within 15 to 30 minutes) the maintenance rate of infusion could be adjusted in increments of 0.1 μg/kg/h or higher to achieve and maintain a Ramsey Sedation Score level of 3 or higher (see FIG. 1).") Example 3, col. 7, l. 67 – col. 8, l. 5 ("For both

			parts of the study, following the initial maintenance infusion, the rate of infusion could have been adjusted in increments of 0.1 µg/kg/h or higher. The infusion rate during intubation was to have been maintained in the range of 0.2 to 0.7 µg/kg/h in order to achieve and maintain a Ramsey Sedation Score of 3 or higher.") *id.* at col. 11, ll. 6-10 ("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."); *c.f.* *id.* at col. 9, ll. 38-40 ("A dexmnedetomidine[*sic*] infusion (0.5 to 0.7 µg/kg/h) was started when the patient arrived in the ICU") (no mention of loading dose as distinct from maintenance dose); *id.* at col. 12, ll. 11-13 ("The dexmedetomidine infusion was maintained between 0.3 and 0.7 µg/kg/h and no additional sedatives were required.") (no mention of distinct loading dose).

NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HOSPIRA, INC., et al. Plaintiffs, v. SANDOZ, INC., et al. Defendants.	:	CIVIL ACTION NO. 09-4591 (MLC) **DRAFT MARKMAN OPINION**

COOPER, District Judge

The Court's Draft Construction of the Term "Intensive Care"

Although the parties used the term "intensive care" in two definitions under United States Patent No. 6,716,867 ("the '867 Patent"), they did not define it. (See id. at 4 ("The parties do not dispute the construction of any terms of the Patents-In-Suit.").) Because the Court has determined that it must define this term before resolving the Motions, it will now construe it.

The Court begins by noting the "'heavy presumption' "that a claim term carries its ordinary and customary meaning." CCS Fitness Inc. v. Brunswick Corp., 288 F.3d 1359, 1366 (Fed. Cir. 2002). The ordinary and customary meaning of a claim term is the meaning a "person of ordinary skill in the art in question" (a "POSITA") would assign such term on the patent's priority date. Phillips v. AWH Corp., 415 F.3d 1303, 1313 (Fed. Cir. 2005). A POSITA is deemed to interpret the claim term in the context of

the entire patent, including the specification. Id. Claims terms carry their ordinary and customary meanings unless otherwise indicated in the patent specification or file history. Wolverine Worldwide, Inc. v. Nike, Inc., 38 F.3d 1192, 1196 (Fed. Cir. 1994).

"To ascertain the scope and meaning of the asserted claims, we look to the words of the claims themselves, the specification, the prosecution history, and any relevant extrinsic evidence." Retractable Techs., Inc. v. Becton, Dicksinon & Co., 653 F.3d 1296, 1303 (Fed. Cir. 2011), rehearing and rehearing en banc denied, 659 F.3d 1369. The Court first looks to the intrinsic evidence of record, which includes the patent's claims, specification, and complete prosecution history. Markman, 52 F.3d at 979. Such intrinsic evidence is the most significant source of the legally operative meaning of disputed claim language. Vitronic Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1583 (Fed. Cir. 1996). The specification is "always highly relevant to the claim construction analysis" and is "the single best guide to the meaning of a disputed term." Honeywell Int'l, Inc. v. ITT Indus., Inc., 452 F.3d 1312, 1318 (Fed. Cir. 2006) (internal quotation marks omitted). The specification may contain an intentional disclaimer or a disavowal of claim scope by the inventor, whereby the inventor's intention, expressed in the specification, is dispositive. Phillips, 415 F.3d at 1316.

It is, however, improper to read a limitation from the specification into the claims. Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1326 (Fed. Cir. 2002).

In some instances, the ordinary meaning of claim language, as understood by a POSITA, will be readily apparent to the Court after reviewing the intrinsic evidence. In such instances, claim construction will involve simply applying the widely accepted meanings of commonly understood words. Phillips, 415 F.3d at 1314. In other circumstances, however, the Court may consider extrinsic evidence, such as "expert and inventor testimony, dictionaries, and learned treatises." Id. In general, such evidence is less reliable than its intrinsic counterparts. Id. at 1318. Notably, "heavy reliance on the dictionary divorced from the intrinsic evidence risks transforming the meaning of the claim term to the artisan into the meaning of the term in the abstract, out of its particular context, which is the specification." Id. at 1321. Further, unsupported assertions by experts as to the definition of a claim term are not useful, and the after-the-fact testimony of the inventor is accorded little if any weight in the claim construction inquiry. Id. at 1318.

The term that actually appears in the '867 Patent claims is "intensive care unit." The parties have stipulated that an "intensive care unit" is "any setting that provides intensive care", but failed to define "intensive care".

The Court begins its claim construction inquiry by examining the intrinsic evidence of record. While the '867 Patent claims and related prosecution history do not help to define "intensive care", the'867 Patent specification provides some guidance. In the specification, Plaintiffs repeatedly refer to sedating patients that suffer from "critical illness" and sedating "critically ill patients". (See, e.g., '867 Patent at col. 1 at 32, 43.) In Example 3, the specification details sixteen cases of sedation of "critically ill patients", describing Phase III trials of dexmedetomidine and "the benefits of dexmedetomidine sedation in critically ill patients." (Id. at col. 8 at line 47 - col. 13 at line 54.) The specification provides that each of the sixteen "critically ill" patients was admitted to an "ICU", i.e., an intensive care unit, either preoperatively or postoperatively, and underwent some form of surgery. (Id.) The specification does not, however, disclose whether these patients underwent surgery because they were "critically ill" or whether they were considered"critically ill" because they underwent surgery. It also fails to disclose the type of nursing care provided to these patients or, more generally, the quality of perioperative care provided, except inasmuch as it discloses the administration of dexmedetomidine, analgesics, and other sedatives. (Id.)

Because examination of the intrinsic evidence does not render a clear definition of "intensive care", the Court next turns to extrinsic evidence. During discovery, the parties solicited deposition regarding the definition of "intensive care". Romeo Bachand, one of the named inventors of the '867 Patent, testified that "intensive care is a unit or a place where people get total care, human care, not procedural care." (Dkt. entry no. 229-12, Bachand Dep. at 164.) He explained that "intensive care[,] by its meaning in the [1990s] . . . had to do with care, and the care was with generally the ratio of patients to nurses taking care of the total patient." (Id. at 162.) Bachand further explained that preoperative and postoperative surgical care are more closely related to the underlying surgical procedure than to intensive care. (Id. at 163.)

Plaintiffs' expert witness, Michael Ramsey, M.D., testified that a "setting that provides intensive care" "would be an area where the patient is intensively monitored for a period of time until the condition that had taken the patient to that unit had resolved or the need for intensive care monitoring, intensive monitoring had passed." (Dkt. entry no. 229-7, Ramsay Dep. at 64.) Ramsay defined "intensive monitoring" as "[o]ne-on-one or two-to-one nursing care, continual monitoring of vital signs, immediate availability of support systems." (Id. at 65.) He testified that a patient could receive such monitoring in many

areas of a hospital, including an intensive care unit, an operating room, or a postoperative recovery area. (Id. at 67-68; dkt. entry no. 229-8, Ramsey Dep. II at 209-10.)

The Sandoz Companies' expert witness, Jesse B. Hall, M.D., opined that critical care settings are defined more so "by the nature of the patient than by the label over the geographic location in the hospital." (Dkt. entry no. 228-2, Ex. E, Hall Dep. at 24.) He stated:

> [I]f a patient is critically ill and is in the emergency department but must wait six hours for a bed to be available, we don't say they are denied critical care management while they're in the emergency room. The facility can be turned to that purpose for that patient's needs.
>
> The same thing occurs in the recovery room when there isn't an ICU bed or perhaps the ICUs need to be decompressed. It's common to just change the nursing ratios to make the circumstance of adequate critical care environment because the physicians can go there as needed, and the monitoring equipment exists to ahieve the same endpoints. It becomes a nursing coverage issue more than anything else.

(Id. at 22.) Hall clarified that patients could thus receive intensive care in emergency rooms and postoperative recovery rooms. (Id. at 23.)

The Court also sua sponte reviewed information provided by dictionaries and treatises. The Court, specifically, reviewed information in THE MERCK MANUAL OF DIAGNOSIS AND TREATMENT, 19th ed. ("The Merck Manual") and STEDMAN'S MEDICAL DICTIONARY ("Stedman's"). The Merck Manual does not provide an explicit definition of

"intensive care"; indeed, the index entry for "intensive care" states only "see Critically ill patient". THE MERCK MANUAL OF DIAGNOSIS AND TREATMENT 3640 (Robert S. Porter, MD, et al. eds., 19th ed., 2011). The main entry for that section, i.e., "Critical Care Medicine", provides:

> Critical care medicine specializes in caring for the most seriously ill patients. These patients are best treated in an ICU staffed by experienced personnel. . . . ICUs have a high nurse:patient ratio to provide the necessary high intensity of service, including treatment and monitoring of physiologic parameters.
>
> Supportive care for the ICU patient includes provision of adequate nutrition and prevention of infection, stress ulcers and gastritis, and pulmonary embolism. Because 15 to 25% of patients admitted to the ICUs die there, physicians should know how to minimize suffering help dying patients maintain dignity.

Id. at 2243-44. The rest of that section sets forth the methods for procedures used to monitor and treat critically ill patients. See id. at 2243-2302.

Stedman's defines "intensive care" as "management and care of critically ill patients". STEDMAN'S MEDICAL DICTIONARY 315 (28th ed., 2006). It defines "critical" as "[d]enoting a morbid condition in which death is possible." Id. at 462. It also defines an "intensive care unit" as "a hospital facility for provision of intensive nursing and medical care of critically ill patients, characterized by the high quality and quantity of continuous nursing and medical supervision and by use of

sophisticated monitoring and resuscitative equipment". Id. at 2067 (emphasis added).

Upon consideration of this evidence, and placing considerable weight on the intrinsic evidence, i.e., on the specification of the '867 Patent, the Court has determined that the term "intensive care" has two important aspects. First, First, "intensive care" involves "critically ill", patients. (See '867 Patent, col. 1 at line 32, 43, col. 8 at line 47 - col. 13 at line 54). See also MERCK MANUAL OF DIAGNOSIS AND TREATMENT 2243-44; STEDMAN'S MEDICAL DICTIONARY 315, 462, 2067. Such "critically ill" patients are typically "the most seriously ill patients" who undergo surgery or other major medical procedures. (See '867 Patent, col. 8 at line 47 - col. 13 at line 54). See also STEDMAN'S MEDICAL DICTIONARY 315, 462. These patients may die, either as a result of underlying medical conditions or as a result of the treatment for those conditions. (See '867 Patent, col. 8 at line 47 - col. 13 at line 54). See also STEDMAN'S MEDICAL DICTIONARY 315, 462.

Second, intensive care is characterized by ongoing medical supervision. MERCK MANUAL OF DIAGNOSIS AND TREATMENT 2243-44. Such supervision typically includes a high nurse-to-patient ratio and continuous nursing care. (Bachand Dep. at 162-64; Hall Dep. at 22-23 (noting that intensive care is characterized as "a nursing coverage issue more than anything else.").) See also MERCK MANUAL

OF DIAGNOSIS AND TREATMENT 2243. This supervision generally includes monitoring. Id.

The Court will thus construe the term "intensive care" as follows:

> care provided to critically ill patients, typically characterized by high nursing-to-patient ratios, continuous medical supervision, and continuous monitoring.

[DRAFT - NOT SIGNED]

MARY L. COOPER
United States District Judge

STEDMAN'S CONCISE

MEDICAL DICTIONARY FOR THE HEALTH PROFESSIONS

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blood; usually connotes abnormally large concentrations of insulin in the circulating blood.

in•su•lin-like ac•tiv•i•ty (ILA) a measure of substances, usually in plasma, that exert biologic effects similar to those of insulin in various bioassays; sometimes used as a measure of plasma insulin concentrations; always gives higher values than immunochemical techniques for the measurement of insulin.

in•su•lin-like growth fac•tors (IGF) peptides whose formation is stimulated by growth hormone. These peptides bring about peripheral tissue effects of that hormone and have high (about 70%) homology to human insulin.

in•su•lin•o•gen•e•sis (in'sŭ-lin-ō-jen'ĕ-sis) production of insulin. [insulin + G. *genesis*, production]

in•su•lin•o•gen•ic, in•su•lo•gen•ic (in'sŭ-lin-ō-jen'ik, in'sŭ-lō-jen'ik) relating to insulinogenesis.

in•su•li•no•ma (in'sŭ-li-nō'mă) an islet cell adenoma that secretes insulin. SYN insuloma.

in•su•lin re•cep•tor sub•strate-1 (IRS-1) a cytoplasmic protein that is a direct substrate of the activated insulin receptor kinase. Insulin exposure results in its rapid phosphorylation at multiple tyrosine residues. Its phosphorylated sites associate with high affinity to certain cellular proteins. IRS-1 thus acts as an adaptor molecule that links the receptor kinase to various cellular activities regulated by insulin. IRS-1 is also phosphorylated after stimulation by insulinlike growth factor-1 and several interleukins.

in•su•lin re•sis•tance diminished effectiveness of insulin in lowering blood sugar levels; arbitrarily defined as requiring 200 units or more of insulin per day to prevent hyperglycemia or ketosis; usually due to insulin binding by antibodies, but abnormalities in insulin receptors on cell surfaces also occur; associated with obesity, ketoacidosis, infection, and certain rare conditions.

in•su•lin shock severe hypoglycemia produced by administration of insulin, manifested by sweating, tremor, anxiety, vertigo, and diplopia, followed by delirium, convulsions, and collapse.

in•su•li•tis (in'sŭ-lī'tis) inflammation of the islands of Langerhans, with lymphocytic infiltration which may result from viral infection and be the initial lesion of insulin-dependent diabetes mellitus. [L. *insula*, island, + *-itis*, inflammation]

in•su•lo•ma (in-sŭ-lō'mă) SYN insulinoma. [L. *insula*, island, + *-oma*, tumor]

in•sult (in'sŭlt) an injury, attack, or trauma. [LL. *insultus*, fr L. *insulto*, to spring upon]

in•sus•cep•ti•bil•i•ty (in'sŭ-sep'ti-bil'i-tē) SYN immunity. [L. *suscipio*, pp. *-ceptus*, to take upon one, fr. *sub*, under, + *capio*, to take]

in•te•gra•tion (in-tĕ-grā'shŭn) **1.** the state of being combined, or the process of combining, into a complete and harmonious whole. **2.** PHYSIOLOGY the process of building up, as by accretion, anabolism, etc. **3.** MATHEMATICS the process of ascertaining a function from its differential. **4.** MOLECULAR BIOLOGY a recombination event in which a genetic element is inserted. [L. *integro*, pp. *-atus*, to make whole, fr. *integer*, whole]

in•teg•ri•ty (in-teg'ri-tē) soundness or completeness of structure; a sound or unimpaired condition.

in•teg•u•ment (in-teg'yu-ment) **1.** the enveloping membrane of the body; includes, in addition to the epidermis and dermis, all of the derivatives of the epidermis, e.g., hairs, nails, sudoriferous and sebaceous glands, and mammary glands. **2.** the rind, capsule, or covering of any body or part. SYN integumentum commune [TA], tegument. [L. *integumentum*, a covering, fr. *in-tego*, to cover]

in•teg•u•men•ta•ry (in-teg-yu-men'tă-rē) relating to the integument. SEE ALSO cutaneous, dermal.

in•teg•u•men•tum com•mune (in-teg-yu-men' tŭm kō-moo'nē) [TA] SYN integument.

in•tel•lec•tu•al•i•za•tion (in-te-lek'choo-ăl-i-zā' shŭn) an unconscious defense mechanism in which reasoning, logic, or focusing on and verbalizing intellectual minutiae is used in an attempt to avoid confrontation with an objectionable impulse, affect, or interpersonal situation. [L. *intellectus*, perception, discernment]

in•tel•li•gence (in-tel'i-jens) **1.** an individual's aggregate capacity to act purposefully, think rationally, and deal effectively with the environment, especially in meeting challenges and solving problems. **2.** PSYCHOLOGY an individual's relative standing on two quantitative indices, measured intelligence and effectiveness of adaptive behavior; a quantitative score or similar index on both indices constitutes the operational definition of intelligence. [L. *intelligentia*]

in•tel•li•gence quo•tient (IQ) the psychologist's index of intelligence as one part of a two-part determination, the other part being an index of adaptive behavior. IQ is ordinarily expressed as a ratio between the person's score on a given test and the score which the average individual of comparable age attained on the same test.

in•ten•si•ty (in-ten'si-tē) marked tension; great activity; often used simply to denote a measure of the degree or amount of some quality. [L. *intendo*, pp. *-tensus*, to stretch out]

in•ten•sive care u•nit (ICU) a hospital facility for provision of intensive nursing and medical care of critically ill patients, characterized by high quality and quantity of continuous nursing and medical supervision and by use of sophisticated monitoring and resuscitative equipment; may be organized for the care of specific patient groups, e.g., neonatal or newborn ICU, neurological ICU, pulmonary ICU. SYN critical care unit.

in•ten•tion (in-ten'shŭn) **1.** an objective. **2.** SURGERY a process or operation. [L. *intentio*, a stretching out; intention]

in•ten•tion spasm a spasmodic contraction of the muscles occurring when a voluntary movement is attempted.

in•ten•tion-to-treat an•al•y•sis method of analyzing results of a randomized controlled trial that includes in the analysis all the cases that should have received a treatment regimen but for whatever reason did not do so. All cases allocated to each arm of the trial are analyzed together as representing that treatment arm, whether or not they received or completed the prescribed regimen.

in•ten•tion trem•or a tremor that occurs during the performance of precise voluntary movements, caused by disorders of the cerebellum or its connections. SYN volitional tremor (2).

inter- among, between. [L. *inter*, between]

in•ter•ac•tion (int'er-ak'shŭn) **1.** the reciprocal action between two entities in a common envi-

Robert E. Rothenberg, M.D., F.A.C.S.

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insomnia Sleeplessness; usually referring to sleeplessness of unknown origin, not that due to illness or disease.
inspection Examination with the eyes, such as the visual *inspection* of a rash.
inspiration The breathing in of air into the lungs; inhalation.
inspiratory capacity The amount of air that can be breathed in after completely breathing out; a guide to lung efficiency.
inspissated Thickened; hardened as a result of being dried out, as wax in the ears.
instability Emotional unbalance; lack of stability.
instep The arch of the foot.
instill To introduce a liquid, such as the *instillation* of drops into an eye.
instinct The primitive, unconscious driving forces, such as the instinct to live, the instinct to reproduce, etc.
instrumentation Treatment by use of instruments.
insufficiency The condition of being inadequate for a given function, e.g., cardiac *insufficiency*.
insufflate To blow a vapor or powder into a part of the body, such as the *insufflation* of powder into the vagina in the treatment of certain vaginal inflammations.
insulate To protect against.
insulin A hormone produced in the cells of the pancreas. When secreted into the bloodstream, it permits the metabolism and utilization of sugar. An insufficient secretion of insulin causes diabetes mellitus. Too much insulin secretion or intake causes hypoglycemia (too little sugar in the blood).
insulinoma A tumor of the insulin producing cells of the pancreas. This leads to too much insulin secretion.
insulin shock A state of shock, often with a convulsion and unconsciousness, brought about by too much insulin; also known as *hypoglycemic shock*.
insult Damage to an organ or part. Trauma.
insusceptibility Immunity.
integration The process by which various functions are coordinated so as to result in a well-organized whole.
integument Skin; the covering of an organ.
intellect The reasoning faculty; the mind.
intelligence quotient (I.Q.) The ratio of a person's mental age to his chronological age, determined by giving psychological tests. I.Q. levels include the genius, the highly intelligent, the normally intelligent, the below average intellect, the moron, the imbecile, the idiot, etc.
intemperance Excessive drinking; overindulgence in food or alcohol.
intensity 1. The degree of power or strength of a process, such as the *intensity* of a light ray. 2. Feeling something or somebody very strongly. 3. Degree of reaction.
Intensive Care Unit (ICU) A separate area in the hospital where extremely sick patients are cared for. The ICUs are manned 24 hours a day by physicians and specially trained nurses. They also are equipped with life-support apparatus.
intensivist A physician who specializes in caring for the critically ill, such as patients who are in Intensive Care Units.
intention tremor A palsy or shaking of the hands on attempting to perform some purposeful movement, such as writing.
inter- A prefix signifying between.
interaction The result when two or more ingredients combine to cause one action.
interarticular Between two joints.
interatrial Between the two atria (auricles) of the heart.
intercellular tissue The area between the cells.
intercondylar Between the con-

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Of Diagnosis and Therapy

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Preface

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right atrial myxomas or in teratomas
terior mediastinal masses. Myxomas
mes diagnosed when tumor cells are
surgically removed embolus
mias and heart failure with features
s sclerosis suggest rhabdomyomas
s. New cardiac symptoms and signs
t with a known extracardiac cancer
rdiac metastases. Chest x-ray may
re changes in the cardiac silhouette

t

primary: Excision
nt primary: Palliation
ic: Depends on tumor origin

nt of benign primary tumors is
xcision followed by serial echo-
hy over 5 to 6 yr to monitor for re-
umors are excised unless another
g, dementia) contraindicates sur-
gery is usually curative (95%
3 yr). Exceptions are rhabdomyo-
of which regress spontaneously
require treatment, and pericardial
which may require urgent pericar-
Patients with fibroelastoma may
valvular repair or replacement.
domyomas or fibromas are multi-
al excision is usually ineffective;
sis is poor after the first year of
l at 5 yr may be as low as 15%.
t of malignant primary tumors is
ative (eg, radiation therapy, che-
management of complications)
gnosis is poor.
t of metastatic cardiac tumors
tumor origin. It may include
motherapy or palliation.

SECTION 16

Critical Care Medicine

222 Approach to the Critically Ill Patient

Critical care medicine specializes in caring for the most seriously ill patients. These patients are best treated in an ICU staffed by experienced personnel. Some hospitals maintain separate units for special populations (eg, cardiac, surgical, neurologic, pediatric, or neonatal patients). ICUs have a high nurse:patient ratio to provide the necessary high intensity

of service, including treatment and monitoring of physiologic parameters.

Supportive care for the ICU patient includes provision of adequate nutrition (see p. 21) and prevention of infection, stress ulcers and gastritis (see p. 131), and pulmonary embolism (see p. 1920). Because 15 to 25% of patients admitted to ICUs die there, physicians should know how to minimize suffering and help dying patients maintain dignity (see p. 3480).

PATIENT MONITORING AND TESTING

Some monitoring is manual (ie, by direct observation and physical examination) and intermittent, with the frequency depending on the patient's illness. This monitoring usually includes measurement of vital signs (temperature, BP, pulse, and respiration rate), quantification of all fluid intake and output, and often daily weight. BP may be recorded by an automated sphygmomanometer; a transcutaneous sensor for pulse oximetry is used as well.

Other monitoring is ongoing and continuous, provided by complex devices that require special training and experience to operate. Most such devices generate an alarm if certain physiologic parameters are exceeded. Every ICU should strictly follow protocols for investigating alarms.

Blood Tests

Although frequent blood draws can destroy veins, cause pain, and lead to anemia, ICU patients typically have routine daily blood tests to help detect problems early. Generally, patients need a daily set of electrolytes and a CBC. Patients with arrhythmias should also have Mg, phosphate, and Ca levels measured. Patients receiving TPN need weekly liver enzymes and coagulation profiles. Other tests (eg, blood culture for fever, CBC after a bleeding episode) are done as needed.

Point-of-care testing uses miniaturized, highly automated devices to do certain blood tests at the patient's bedside or unit (particularly ICU, emergency department, and operating room). Commonly available tests include blood chemistries, glucose, ABGs, CBC, cardiac markers, and coagulation tests. Many are done in < 2 min and require < 0.5 mL blood.

Cardiac Monitoring

Most critical care patients have cardiac activity monitored by a 3-lead system; signals are usually sent to a central monitoring station by a small radio transmitter worn by the patient. Automated systems generate alarms for abnormal rates and rhythms and store abnormal tracings for subsequent review.

Some specialized cardiac monitors track advanced parameters associated with coronary ischemia, although their clinical benefit is unclear. These parameters include continuous ST-segment monitoring and heart rate variability. Loss of normal beat-to-beat variability signals a reduction in autonomic activity and possibly coronary ischemia and increased risk of death.

Pulmonary Artery Catheter Monitoring

Use of a pulmonary artery catheter (PAC) is becoming less common in ICU patients. This balloon-tipped, flow-directed catheter is inserted via central veins through the right side of the heart into the pulmonary artery. The catheter typically contains several ports that can monitor pressure or inject fluids. Some PACs also include a sensor to measure central (mixed) venous O_2 saturation. Data from PACs are used mainly to determine cardiac output and preload. Preload is most commonly estimated by the pulmonary artery occlusion pressure (see p. 2245). However, preload may be more accurately determined by right ventricular end-diastolic volume, which is measured using fast-response thermistors gated to heart rate.

Despite longstanding use, PACs have not been shown to reduce morbidity and mortality. Rather, PAC use has been associated with excess mortality. This finding may be explained by complications of PAC use and misinterpretation of the data obtained. Nevertheless, some physicians believe PACs, when combined with other objective and clinical data, aid in the management of certain critically ill patients. As with many physiologic measurements, a changing trend is typically more significant than a single abnormal value. Possible indications for PACs are listed in Table 222–1.

Procedure: The PAC is inserted through a special catheter in the subclavian or internal jugular vein with the balloon deflated. Once the catheter tip reaches the superior vena cava, partial inflation of the balloon permits blood flow to guide the catheter. The position of the catheter tip is usually determined by pressure monitoring (see Table 222–2 for intracardiac and great vessel pressures) or occasionally by fluoroscopy. Entry into the right ventricle is indicated by a sudden increase in systolic pressure to about 30 mm Hg; diastolic pressure remains unchanged from

Table 222–1. POTENTIAL INDICATIONS FOR PULMONARY ARTERY CATHETERIZATION

Cardiac disorders
Acute valvular regurgitation
Cardiac tamponade
Complicated heart failure
Complicated MI
Ventricular septal rupture
Hemodynamic instability*
Assessment of volume status
Shock
Hemodynamic monitoring
Cardiac surgery
Postoperative care in critically ill patients
Surgery and postoperative care in patients with significant heart disease
Pulmonary disorders
Complicated pulmonary embolism
Pulmonary hypertension

*Particularly if inotropic drugs are required.

right atrial or vena caval pressure. When the catheter enters the pulmonary artery, systolic pressure does not change, but diastolic pressure rises above right ventricular end-diastolic pressure or central venous pressure (CVP); ie, the pulse pressure narrows. Further movement of the catheter wedges the balloon in a distal pulmonary artery. A chest x-ray confirms proper placement.

The systolic pressure (normal, 15 to 30 mm Hg) and diastolic pressure (normal, 5 to 13 mm Hg) are recorded with the catheter balloon deflated. The diastolic pressure corresponds well to the occlusion pressure, although diastolic pressure can exceed occlusion pressure when pulmonary vascular resistance is elevated secondary to primary pulmonary disease (eg, pulmonary fibrosis, pulmonary hypertension).

Pulmonary artery occlusion pressure (PAOP): With the balloon inflated, pressure at the tip of the catheter reflects the static back pressure of the pulmonary veins. The balloon must not remain inflated for > 30 sec to prevent pulmonary infarction. Normally, PAOP approximates left atrial pressure, which in turn approximates left ventricular end-diastolic pressure (LVEDP). LVEDP reflects left ventricular end-diastolic volume (LVEDV). The LVEDV represents preload, which is the actual target parameter. Many factors cause PAOP to reflect LVEDV inaccurately. These factors include mitral stenosis, high levels of positive end-expiratory pressure (> 10 cm H_2O), and changes in left ventricular compliance (eg, due to MI, pericardial effusion, or increased afterload). Technical difficulties result from excessive balloon inflation, improper catheter position, alveolar pressure exceeding pulmonary venous pressure, or severe pulmonary hypertension (which may make the balloon difficult to wedge).

Elevated PAOP occurs in left-sided heart failure. Decreased PAOP occurs in hypovolemia or decreased preload.

Mixed venous oxygenation: Mixed venous blood comprises blood from the superior and inferior vena cava that has passed through the right heart to the pulmonary artery. The blood may be sampled from the distal port of the PAC, but some catheters have embedded fiberoptic sensors that directly measure O_2 saturation.

Table 222–2. NORMAL PRESSURES IN THE HEART AND GREAT VESSELS

TYPE OF PRESSURE	AVERAGE (mm Hg)	RANGE (mm Hg)
Right atrium	3	0–8
Right ventricle		
Peak-systolic	25	15–30
End-diastolic	4	0–8
Pulmonary artery		
Mean	15	9–16
Peak-systolic	25	15–30
End-diastolic	9	4–14
Pulmonary artery occlusion		
Mean	9	2–12
Left atrium		
Mean	8	2–12
A wave	10	4–16
V wave	13	6–12
Left ventricle		
Peak-systolic	130	90–140
End-diastolic	9	5–12
Brachial artery		
Mean	85	70–150
Peak-systolic	130	90–140
End-diastolic	70	60–90

Adapted from Fowler NO: *Cardiac Diagnosis and Treatment*, ed 3. Philadelphia, JB Lippincott, 1980, p. 11.

Causes of low mixed venous O_2 content ($SmvO_2$) include anemia, pulmonary disease, carboxyhemoglobin, low cardiac output, and increased tissue metabolic needs. The ratio of SaO_2 to ($SaO_2 - SmvO_2$) determines the adequacy of O_2 delivery. The ideal ratio is 4:1, whereas 2:1 is the minimum acceptable ratio to maintain aerobic metabolic needs.

Cardiac output: Cardiac output (CO) is measured by intermittent bolus injection of ice water or, in new catheters, continuous warm thermodilution. The cardiac index divides the CO by body surface area to correct for patient size (see Table 222–3).

Other variables can be calculated from CO. They include systemic and pulmonary vascular resistance and right ventricular stroke work (RVSW) and left ventricular stroke work (LVSW).

Complications and precautions: PACs may be difficult to insert. Cardiac arrhythmias are the most common complication. Pulmonary infarction secondary to overinflated or permanently wedged balloons, pulmonary artery perforation, intracardiac perforation, valvular injury, and endocarditis may occur. Rarely, the catheter may curl into a knot within the right ventricle (especially in patients with heart failure, cardiomyopathy, or increased pulmonary pressure).

Pulmonary artery rupture occurs in <0.1% of PAC insertions. This catastrophic complication is often fatal and occurs immediately on wedging the catheter either initially or during a subsequent occlusion pressure check. Thus, many physicians prefer to monitor pulmonary artery diastolic pressures rather than occlusion pressures.

Table 222–3. NORMAL VALUES FOR CARDIAC INDEX AND RELATED MEASUREMENTS

MEASUREMENT	UNITS ± SD
O_2 uptake	143 ± 14.3 mL/min/m^2
Arteriovenous O_2 difference	4.1 ± 0.6 dL
Cardiac index	3.5 ± 0.7 L/min/m^2
Stroke index	46 ± 8.1 mL/beat/m^2
Total systemic resistance	1130 ± 178 dynes-sec-cm^{-5}
Total pulmonary resistance	205 ± 51 dynes-sec-cm^{-5}
Pulmonary arteriolar resistance	67 ± 23 dynes-sec-cm^{-5}

SD = standard deviation.

Adapted from Barratt-Boyes BG, Wood EH: Cardiac output and related measurements and pressure values in the right heart and associated vessels, together with an analysis of the hemodynamic response to the inhalation of high oxygen mixtures in healthy subjects. *Journal of Laboratory and Clinical Medicine* 51:72–90, 1958.

Noninvasive Cardiac Output

Other methods of determining CO, such as thoracic bioimpedance and the esophageal Doppler monitor, are being developed to avoid the complications of PACs. Although these methods are potentially useful, neither is yet as reliable as a PAC.

Thoracic bioimpedance: These systems use topical electrodes on the anterior chest and neck to measure electrical impedance of the thorax. This value varies with beat-to-beat changes in thoracic blood volume and hence can estimate CO. The system is harmless and provides values quickly (within 2 to 5 min); however, the technique is very sensitive to alteration of the electrode contact with the patient. Thoracic bioimpedance is more valuable in recognizing changes in a given patient than in precisely measuring CO.

Esophageal Doppler monitor (EDM): This device is a soft 6-mm catheter that is passed nasopharyngeally into the esophagus and positioned behind the heart. A Doppler flow probe at its tip allows continuous monitoring of CO and stroke volume. Unlike the invasive PAC, the EDM does not cause pneumothorax, arrhythmia, or infection. An EDM may actually be more accurate than a PAC in patients with cardiac valvular lesions, septal defects, arrhythmias, or pulmonary hypertension. However, the EDM may lose its waveform with only a slight positional change and produce dampened, inaccurate readings.

Intracranial Pressure Monitoring

Intracranial pressure (ICP) monitoring is standard for patients with severe closed head injury. These devices are used to optimize cerebral perfusion pressure (mean arterial pressure minus intracranial pressure). Typically, the cerebral perfusion pressure should be kept > 60 mm Hg.

Several types of ICP monitors are available. The most useful method places a catheter through the skull into a cerebral ventricle (ventriculostomy catheter). This device is preferred because the catheter can also drain CSF and hence decrease ICP. However, the ventriculostomy is also the most invasive method, has the highest infection rate, and is the most difficult to place. Occasionally, the ventriculostomy becomes occluded due to severe brain edema.

Other types of intracranial devices include an intraparenchymal monitor and an epidural bolt. Of these, the intraparenchymal monitor is more commonly used. All ICP devices should usually be changed or removed after 5 to 7 days because infection is a risk.

Other Types of Monitoring

Sublingual capnometry uses a similar correlation between elevated sublingual P_{CO_2} and systemic hypoperfusion to monitor shock states using a noninvasive sensor placed under the tongue. This device is easier to use than gastric tonometry and responds quickly to perfusion changes with resuscitation.

Tissue spectroscopy uses a noninvasive near infrared (NIR) sensor usually placed on the skin above the target tissue to monitor mitochondrial cytochrome a,a redox states, which reflect tissue perfusion. NIR may help diagnose acute compartment syndromes (eg, trauma) or ischemia after free tissue transfer and may be helpful in postoperative monitoring of lower-extremity vascular bypass grafts. NIR monitoring of small-bowel pH may be used to gauge the adequacy of resuscitation.

SCORING SYSTEMS

Several scoring systems have been developed to grade the severity of illness in critically ill patients. These systems are moderately accurate in predicting individual survival. However, these systems are more valuable for monitoring quality of care and for conducting research studies because they allow comparison of outcomes among groups of critically ill patients with similar illness severity.

The most common system is the 2nd version of the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score introduced in 1985. It generates a point score ranging from 0 to 71 based on 12 physiologic variables, age, and underlying health (see Table 222–4). The APACHE III system was developed in 1991. This system is more complex, has 17 physiologic variables, and is somewhat less used. There are many other systems, including the 2nd Simplified Acute Physiology Score (SAPS II) and several mortality probability models.

VASCULAR ACCESS

A number of procedures are used to gain vascular access.

Peripheral Vein Catheterization

Most patients' needs for IV fluid and drugs can be met with a percutaneous peripheral venous catheter. Venous cutdown can be used when percutaneous catheter insertion is not feasible. Typical cutdown sites are the cephalic vein in the arm and the saphenous vein at the ankle.

Common complications (eg, local infection, venous thrombosis, thrombophlebitis, interstitial fluid extravasation) can be reduced by using a meticulous sterile technique during insertion and by replacing or removing the catheters within 72 h.

Central Venous Catheterization

Patients needing secure or long-term vascular access (eg, to receive antibiotics, chemotherapy, or TPN) are best treated with a central venous catheter (CVC). CVCs allow infusion of solutions that are too concentrated or irritating for peripheral veins and allow monitoring of central venous pressure (CVP—see p. 2299).

Procedure: CVCs are inserted using sterile technique and a local anesthetic (eg, 1% lidocaine). The superior vena cava is entered via percutaneous puncture of the subclavian or the internal or external jugular vein or by venous cutdown on the basilic vein. The inferior vena cava may be entered through the common femoral vein percutaneously or by cutdown on the saphenous vein. The choice of site depends on operator preference and patient habitus and ambulatory status. However, femoral venous catheters have a slightly higher rate of complications than those above the waist. Also, during cardiac arrest, fluid and drugs given through a femoral or saphenous vein CVC often fail to circulate above the diaphragm because of the increased intrathoracic pressure generated by CPR. In this case, a subclavian or internal jugular approach may be preferred.

If possible, the patient's coagulation status and platelet count should be normalized before CVC insertion. Percutaneous femoral lines must be inserted below the inguinal ligament. Otherwise, laceration of the external iliac vein or artery above the inguinal ligament may result in retroperitoneal hemorrhage; external compression of these vessels is nearly impossible. The subclavian vein also is not

Stress, agitation, and brain failure in critical care medicine

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THE TERM "AGITATION" describes a syndrome of excessive motor activity, usually nonpurposeful and associated with internal tension.[1] For intensivists, agitation is not so much a diagnosis, but a consequence of more fundamental etiologies 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.[2] 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 relative-

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ly 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 technologic 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.

PATHOPHYSIOLOGY OF BRAIN FAILURE AND AGITATION

A major function of the central nervous system (CNS) is the processing of incoming stimuli in such a way that coordinated and appropriate motor responses occur.[3] Brain metabolism is served by complex mechanisms that ensure reliable access to nutrients. Since the brain has no stores of glucose, cell-ular metabolism depends on the content and continuity of blood flow. Effective metabolic function is especially important for neurotransmitter synthesis, transport, and discharge, and so metabolism is a key concept in normal neurotransmitter function. When metabolic homeostasis is interrupted or distorted, various degrees of "brain failure" can occur.[4] Brain failure is just as much a relevant ICU organ insufficiency as is renal or hepatic failure, and agitation can be an ominous neurobehavioral sign of acute pathophysiology. When agitation accompanies brain failure in a critical care setting, there exists a failure to integrate cerebral functioning that constitutes a true emergency (Fig 1).

The major cause of integrative brain failure is a hemodynamic or metabolic decompensation, either intracranial or extracranial (Fig 2). The ICU environment provides a repository of typical predisposing factors of a hemodynamic or metabolic nature, including acute or chronic organic brain vascular insufficiency, endocrine insufficiency, acute or chronic cardiopulmonary decompensations, multiorgan system insufficiency, rel-

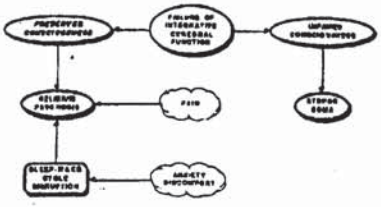

Fig 1. Causes of agitation.

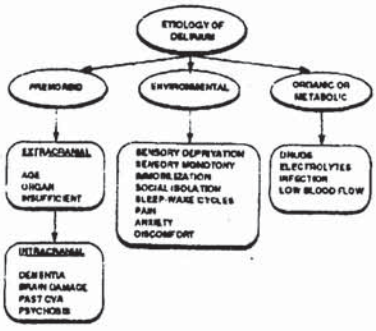

Fig 2. Etiology of delirium.

ative hypoxia, poor tissue perfusion, multimedications, and, finally, disruption of the sleep-wake cycle caused by immobilization, anxiety, and pain.[5] Clinical signs of agitation are likely to be produced when there is an integrative brain failure plus an intense source of sensory stimuli.[6] Environmental stress, although likely to exacerbate integrative brain failure, is rarely a precipitory cause by itself.[2]

The nervous system is unique in the vast complexity of the control actions that it can perform. While the autonomic system mainly deals with smooth muscle activity and glands, the motor axis of the nervous system is responsible for controlling skeletal muscle contractions. The skeletal muscle system can be controlled from many different levels of the CNS, including the spinal cord, reticular substance of the medulla, pons, mesencephalon, basal ganglia, cerebellum, and motor cortex. The lower control regions are primarily concerned with automatic, instantaneous responses of the body to the sensory stimuli, and the higher regions are concerned with deliberate movements controlled by cerebral thought processes. More than 99% of all sensory information is discarded by the brain as irrelevant. After the salient sensory stimuli have been selected, they are channeled through numerous neuronal circuits into proper motor regions of the brain to elicit desired responses. This channeling of stimuli is called the integrative function of the nervous system. The major function of the nervous system is the processing of incoming information in such a way that coordinated and appropriate motor responses occur.

Only a small fraction of selected sensory stimuli elicits an immediate motor response. Much of the remainder is stored as imprinted memory for unconsciously directed control of "learned" motor activities and for cognitive processes. Most of this storage occurs in the cerebral cortex, but the spinal cord can also store small amounts of information. Once imprinted memories have been stored in the nervous system, they become part of the processing mechanism, and the brain constantly compares new sensory experiences with stored memories. Integrative brain functions help to select the important new sensory information and to channel it into appropriate storage areas for future use or into motor areas to cause somatic responses. Agitation is a visual clue that disintegration of normal motor axis integration, with mischanneling of incoming sensory stimuli, is occurring. Short circuits into filogenetically old brain areas such as basal ganglia, reticular formation, vestibular nuclei, and, often, the red nucleus (extrapyramidal system) produce the clinical picture of uncoordinated and nonpurposeful movements. If this failure is severe and widespread, delirium usually occurs first and is followed by various degrees of coma.

Delirium is characterized by global disorders of cognition and wakefulness and by impairment of psychomotor behavior.[6] Major cognitive functions such as perception, deductive reasoning, memory, attention, and orientation are all globally disordered.[5] There is a growing consensus that delirium is a manifestation of cerebral insufficiency, both generalized[7] and focal,[8] accompanied by dysregulation of neurotransmitter systems.[9] Currently favored pathophysiologic mechanisms include 1) a cholinergic-dopaminergic imbalance, 2) dopamine and β-endorphin hyperfunction, 3) increased central noradren-

ergic activity, and 4) damage to intraneuronal enzyme systems.[10,11] Excessive motor activity frequently accompanies severe cases of delirium, and, when this occurs, the resulting constellation of symptoms is called "agitated delirium."

DELIRUM

Potential causes in the ICU

Delirium is a multifactorial syndrome caused by a wide range of metabolic and organic disorders some of which may be unrelated to the nervous system. Most causes of delirium can be grouped into three categories: premorbid physiology, metabolic derangements, and environmental stress. The major predisposing factors in the premorbid state are age, chronic mental illnesses, general level of cerebral competence, stability of interpersonal relationships, substance addition, and chronic hepatic, renal, cardiac, and pulmonary dysfunction. In the elderly, a selective loss of neuronal populations in the frontal cortex, hippocampus, and locus ceruleus and a decrease in acetylcholine activity are thought to account for the increased susceptibility to delirium.[11] Organic or metabolic causes of delirium can include virtually any drug and interactions between drugs. Multimedication regimens combined with blood chemistry imbalances are frequent in hospitalized patients. Accidental and intentional intoxication from overdoses of psychoactive substances occur in psychiatric patient populations. Neuroendocrine crises may be precipitated by chronic corticosteroid therapy after nonspecific stress responses to excessive pain, anxiety, discomfort, infections, vitamin deficiencies, or trauma.

The term "ICU psychosis" was introduced to underline the etiologic significance of psychosocial and psychologic factors in understanding the syndrome. ICU activities around the clock may lead to a patient's loss of orientation to time. Monotonous sensory input in the form of unfamiliar, repetitive, and noisy monitoring equipment; prolonged immobilization with the proverbial "tube or appliance in every orifice;" brief but frequently interrupted "nap" sleep patterns; social isolation; and unfamiliarity with the ICU personnel (who change frequently) eventually contribute to the predelirious state. There is no doubt that environmental factors are contributory and may exacerbate the existing delirium or accelerate the transition from a predelirious state to full-blown delirium, but as a sole primary cause, the ICU environment is largely overemphasized. As is the case with any other organ failure, disintegrated cerebral functioning usually results when severe physiologic and metabolic insults occur and then result in organ system malfunction. When the syndrome is observed after multiple organ system failure, it is an ominous sign of a bad outcome.[12]

The term "psychosis," although integral to the definition, is not an accurate description of the disorder and leads to misleading conclusions. True delirium, in or out of a critical care unit, may exhibit psychotic features such as hallucinations, delusions, and disordered thinking, but it is not a true psychosis. The term psychosis, as used in the psychiatric literature, refers to persistent disorders of brain functioning in which no specific organic factors may be causally related. In true delirium, organic causation is not only present but most often stems from outside the nervous system. Moreover, there is a qualitative difference

between the symptomatology of delirium and of psychoses such as schizophrenia and mania. Symptoms of delirium are extremely random and purposeless, without systematization, while psychotic symptoms are frequently bizarre, but well-organized and consistent. The term "ICU stress delirium" would be more applicable for organic brain syndromes occurring in the ICU.

Clinical presentations

Clinically, delirium is characterized by disorganized thinking, reduced ability to maintain attentiveness, and rambling, irrelevant, or incoherent thought and speech patterns.[5] The delirious patient cannot integrate a coherent stream of thoughts and deduce meaningful information from them. Short-term memory is impaired as a result of a short attention span and perceptual misregistration of incoming stimuli. Memory retention is also defective. A majority of delirious patients will be amnesic following recovery or will preserve small, random "islands of memory." Orientation to time is most often impaired in mild delirium, but orientation of person and place remains intact. As delirium progresses, disorientation to person and place ensues. Fluctuating levels of arousal over the day's course is a central hallmark of delirium and a major diagnostic criterion. The manifestations of delirium associated with sleep–wake cycles, such as disorganized cognitive and attention patterns that fluctuate in reverse day–night cycles, poorly organized delusions and hallucinations, and the presence of lucid intervals, are virtually diagnostic of stress-induced delirium. This symptomatology effectively differentiates delirium from dementia, functional psychosis, and psychogenic dissociative states. Patients exhibiting this stress-induced ICU delirium continually resist restraints and treatment modalities, sometimes to the point of exhaustion. Since this psychomotor agitation syndrome usually occurs in the night hours, it has been termed the "sundown syndrome" by intensive care nurses and is virtually diagnostic of stress-induced delirium.

During the state of delirium, cognition loses its clarity and goal direction. In milder forms of delirium, cognition patterns may be accelerated or slowed, and there are lucid intervals. These patients can sometimes be reasoned with and may trust the reasoning ability of others during confusional states. In severe delirium, however, cognition is totally fragmented and disjointed. The patient is unable to reason deductively or solve problems and cannot perceive reality, even with direction from an unaffected onlooker. Because the delirious patient cannot refit the fragments of cognition, his or her perceptions are altered, leading to the development of delusions and hallucinations. These delusions tend to be individualized and paranoid; that is, the patient misinterprets the actions and events around him or her as life-threatening and potentially harmful. Hallucinations are characteristically fleeting, changeable, and poorly organized. Hallucinations in delirium are usually visual and auditory rather than olfactory, tactile, or kinesthetic. For example, a sound of a falling glass may be mistaken for a pistol shot, or IV catheters may appear to be snakes (misperceptions). The subdued voices of housestaff physicians on rounds, discussing a care plan, may be mistaken for the plotting of some dangerous medical experiment that would result in a patient's death (delusions). In advanced

stages, misperceptions become vivid and the patient may "see" visiting relatives arrive to save him from the medical staff when no one is actually there (hallucinations).

When considering agitation in the ICU, one must always keep in mind the possibility of hypoxia mediated as a primary underlying cause. All possible causes of hypoxemia, as well as an estimation of brain perfusion pressure, must be aggressively investigated. Improvement of brain oxygenation and perfusion is of primary importance in the treatment of any type of psychosis in the hemodynamically compromised patient. Global brain ischemia due to cardiorespiratory failure results in activation of the diencephalic and rhombencephalic areas of the brain, especially the activating reticular formation. This activation manifests as persistent agitation and is most frequently seen after cardiac surgery.[13] This form of agitation is frequently difficult to control by high doses of IV sedatives, and the patient breathes disconjugately with the ventilator. Subacute brain ischemia or marginal brain perfusion, especially in elderly patients, can be an occult cause of delirium.[14,15]

Rational treatment: Phenothiazines and neuroleptics

The phenothiazine and neuroleptic drugs exert an antipsychotic effect by antagonizing dopamine-mediated neurotransmission at the synapses.[16] Phenothiazines also affect the basal ganglia, enhancing the potential for extrapyramidal side effects. The therapeutic effect of the drug is gradually to decrease psychotic symptoms such as hallucinations, delusions, and nonstructured patterns of thought. Higher intellectual function normally remains intact, but the patient's interest in his or her environment is diminished, producing a characteristic flat effect. This class of drugs also exerts a pronounced anxiolytic effect, ameliorating restlessness, but this effect decreases with long-term therapy.

Chlorpromazine

The prototype phenothiazine, chlorpromazine, is an antipsychotic agent with significant sedative properties.[17] Chlorpromazine produces sedation without hypnosis, but it may potentiate the CNS depressive effects of benzodiazepines administered concurrently. Chlorpromazine can be useful in the treatment of the ICU patient with stress-induced delirium, as it acts to resolve disorganized brain chemistry and as a broad-spectrum sedative agent. However, chlorpromazine functions at the expense of some significant side effects. The therapeutic index of chlorpromazine is rather narrow, resulting in a blurred distinction between beneficial and undesirable effects at therapeutic doses. The drug induces a pronounced antihistaminic effect, leading to dry mucous membranes. Patients with disorganized thought processes frequently interpret this effect as thirst and respond with psychogenic polydipsia and symptomatic hyponatremia. Chlorpromazine lowers seizure thresholds and may precipitate seizures in patients prone to them, especially in alcoholics. Electrical activity of the heart is altered, resulting in electrocardiogram (ECG) changes such as of QT and PR interval prolongation, blunting of T waves, and ST segment depression. Effective hemodynamic monitoring is mandatory during the use of this drug. Most ICU indications for chlorpromazine involve intravenous admin-

istration, titrated according to the desired effect with the lowest possible dosage. Chlorpromazine may interfere with other hemodynamically active drugs being administered in the ICU by blocking α-adrenergic and muscarinic receptors, as well as adrenergic agonist activity, which may precipitate tachycardia, vasodilatation, and postural hypotension.[18]

Haloperidol

Haloperidol appears to exert a diffuse, depressive effect at the subcortical, midbrain, and brain-stem reticular formation levels. The precise antipsychotic mechanism is not known. The drug may also inhibit catecholamine receptors and reuptake of various neurotransmitters in the midbrain. Haloperidol produces less sedation than other phenothiazines, having very little effect on heart rate, blood pressure, and respiration. A unique effect of haloperidol is its relatively strong suppression of spontaneous musculoskeletal hyperactivity and behavior that results from hyperdopaminergic brain function without pronounced sedation or hypotension.[19] There appears to be a rather narrow therapeutic range between doses that are therapeutic for antipsychosis and the dose that precipitates extrapyramidal reactions. Currently, IV use is not approved by the FDA, but the drug is commonly given by this mode, and a broad range of experience with it has been reported in the peer-reviewed medical literature.[19-21] The dose and frequency of administration are dependent on the degree of agitation and, to a lesser extent, the patient's age.

Adverse hemodynamic effects are rare in healthy individuals. Unexpected hypotension may occur in hypovolemic patients or patients with low cardiac output. Combined use of lorazepam and haloperidol has been reported to be most effective in combining antipsychotic effects and sedation with a minimum of side effects.[22] Haloperidol may be safer to use in alcohol-related delirium than chlorpromazine. One study[23] showed that haloperidol did not precipitate any untoward side effects when used to treat 36 head trauma patients and 90 patients acutely intoxicated with alcohol. Like chlorpromazine, haloperidol can precipitate extrapyramidal reactions, especially in the initial stages of treatment. These reactions usually consist of Parkinson-like symptoms: drowsiness, lethargy, and a fixed stare. Extrapyramidal symptoms usually reverse rapidly after the administration of benztropine or benzodiazepines and cessation of the drug.[24] Tardive dystonia, oculogyric crisis, torticollis, and trismus are all rare, and most occurrences are dose related. Neuroleptic malignant syndrome may occur with any dose of haloperidol administration, requiring ICU admission and aggressive, titrated life support.

Comorbidities in delirium states

Factors that exacerbate stress in the ICU shorten the time necessary to produce delirium. These major factors contributing to the development of agitation in the ICU are pain, anxiety, and discomfort.

Pain

Most patients who find themselves in ICUs have had an operative or medical procedure that results in pain. Frequently, intubated patients undergoing mechanical ventilation find it almost impossible to communicate

their displeasure, which increases their frustration. The perception of pain exacerbates agitation by stimulating sympathetic centers in the brain, which leads to catecholamine release. Hormonal response to pain results in sodium and water retention due to the secretion of antidiuretic hormone (ADH) and aldosterone and to hyperglycemia from increased cortisol and epinephrine secretions. All of these humoral responses require monitoring in the ICU. In addition, pain manifests itself in the easily recognizable triad of tachycardia, tachypnea, and systolic hypertension, all of which are amenable to ICU monitoring.

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.

Discomfort

Patients forced to lie still for long periods, even though encumbered by indwelling hardware, soon become profoundly uncomfortable and seek more comfortable positions. The need to move about and stretch can become an obsession, especially during sleepless nights, which decreases the patient's ability to cope. Sympathetic stimulation does not necessarily occur, but constant musculoskeletal activity may cause physical exhaustion. Restraining patients usually results in attempts to escape confinement, which exacerbates agitation.

Effective treatment of comorbidities

The effective management of factors that exacerbate ICU delirium, such as pain, anxiety, and discomfort, includes both pharmacologic and nonpharmacologic approaches. Supportive care includes assessing an accurate medical history for evidence of past episodes and hints about successful past treatment, ensuring patient comprehension of invasive monitoring equipment, and providing emotional support and reassurance. Patients who have just arrived in the ICU, especially under emergent circumstances, must not feel that they have completely lost control of their fates. The value of supportive nursing care cannot be overemphasized.[25]

Treatment of pain

There have been major advances in the understanding of pain physiology over the last 10 years. Earlier concepts of a dedicated, simple, spinothalamic pain system are no longer tenable. Much evidence now exists that very complex neural connections involving diverse areas of the nervous system play a part. Pain may be modulated or edited at the spinal cord level, in the periaqueductal gray matter, and at the brain-stem raphe nuclei prior to reaching relays and gating mechanisms in the thalamus on the way to the cerebral cortex. The perception of noxious

stimuli may depend not only on peripheral stimulation and transmission, but also on modulation occurring in spinal cord and higher structures. Accordingly, the subjective sensation of pain can be effectively blocked at the brain level by narcotic analgesics and also at the inflow tract level, which explains the efficacy of spinal or epidural anesthesia.

Normally, agitation caused by pain is treated by analgesics or analgesic sedatives such as morphine sulfate. This class of medication ultimately diminishes the stimulus to secrete epinephrine and norepinephrine and so decreases the end-organ response to these catecholamines. Patients who exhibit an enhanced catecholamine response to pain tend to tolerate well the hemodynamic side effects of the narcotics. Humoral responses such as hypertension and tachypnea tend to counterbalance the side effects of narcotic analgesics, such as hypotension from histamine release and medullary ventilation center depression. Agitation syndromes resulting from pain usually resolve when the primary stimulus disappears.

Morphine sulfate

The most widely used of all narcotic analgesics or sedatives,[26] morphine is very convenient as it may be given by oral, subcutaneous, intrathecal, epidural, intramuscular, and intravenous routes. The drug is easily titrated and reversible with narcotic antagonists. In addition to its sedative action, morphine has profound effects on cardiac hemodynamics. Doses as small as 0.1 to 0.2 mg/kg can produce orthostatic hypotension in normal subjects due to vasodilatation in the splanchnic beds, decreasing preload and filling pressures in the right side of the heart.[27] This vasodilatory effect has been attributed to both histamine release and direct effects from neural mediators. The respiratory depressive effect can be profound and unpredictable. A 10-mg dose of morphine sulfate (0.15 mg/kg) will increase the P_{CO_2} by about 3 torr in normal subjects.[28] Even with these side effects, morphine sulfate remains a highly desirable choice for most analgesia indications. Intrathecal and epidural morphine provides safe and effective analgesia in selected patients when respiratory drive inhibition must be considered.[29] The incidence of iatrogenic inducement of addiction is not clinically significant in ICU applications.

Fentanyl

A synthetic opioid, fentanyl is approximately 7000 times more lipophilic than morphine. This allows it to penetrate biologic membranes rapidly, especially in the brain. Fentanyl is about 200 times more potent than morphine, significantly more rapid-acting (1–2 minutes), and of shorter duration (30–40 minutes). Compared to morphine, fentanyl promotes minimal histamine release and exhibits significantly less effect on cardiac dynamics. Its affinity for fat can lead to its accumulation during prolonged use, but this accumulation ultimately leaches out after discontinuation of the drug. Thus, repeated doses of the drug tend to exhibit a longer duration of action. Like morphine, it is quickly reversible with narcotic antagonists. Fentanyl combines an analgesic and anxiolytic effect, but it is much more effective as an analgesic than sedative in low doses. Equianalgesic doses of morphine and fentanyl produce about the same respiratory de-

pression. The addition of a benzodiazepine has been reported to produce decreased cardiac output, decreased blood pressure, and peripheral resistance out of proportion to the effect of either drug alone.[30] Occasionally, the rapid administration of high doses of fentanyl has resulted in muscular and glottic rigidity during the induction of anesthesia. This complication is reversible with naloxone or succinyl choline.[31,32]

Ketorolac

Ketorolac is a parenteral nonsteroidal antiinflammatory agent that has almost pure analgesic activity. Ketorolac at 60 mg intramuscularly is 800 times as potent as aspirin and approximately equal in analgesic effect to 10 to 12 mg of morphine sulfate.[33,34] However, ketorolac has significantly less respiratory and hemodynamic effects than morphine. There is a need for a "pure" (nonnarcotic) analgesic in hemodynamically unstable patients, in whom the side effects of narcotic analgesics would be poorly tolerated. Incisional pain prevents postoperative patients with upper midline abdominal incisions from coughing effectively, which results in a significant decrease in forced expiratory volume and compromising clearance of tracheal secretions. A pure analgesic may decrease the risk of nosocomial pneumonia by allowing patients to clear their secretions more effectively with less risk of respiratory depression. Moreover, ICU patients in heart failure who must undergo painful procedures such as invasive vascular catheterization, chest tube thoracostomy, or intraaortic balloon placement poorly tolerate narcotic side effects. Because of the CNS-depressant side effects of narcotic analgesics, acutely ill patients in pain cannot be given medications that might affect their ability to give informed consent.

Ketorolac is usually administered by the intramuscular route, but critical care patients generally tolerate IM injections poorly. Poor peripheral tissue perfusion in patients with cardiac decompensations provides erratic and ineffective absorption of medication deposited outside the intravascular space. There is evidence in the literature that the intravenous administration of ketorolac is safe and effective.[35] IV administration would presumably allow more rapid onset of action, closer titration, and more predictability of response.[36] Clinical trials are in progress at the authors' institution to test the feasibility and safety of ketorolac in the intravenous route for ICU patients.

α–2 Agonists

α-2 Adrenoreceptors are members of the guanine nucleotide-binding, protein-coupled family of membrane receptors[37] and are located both centrally and peripherally. Their function is to inhibit norepinephrine release from presynaptic junctions by several negative feedback mechanisms. These effector mechanisms include the inhibition of adenylate cyclase that attenuates the stimulation of cAMP-dependent protein kinase[38]; the opening of outwardly directed potassium channels, which hyperpolarizes neuronal membranes[39] and; the inhibition of calcium channels, which decreases the entry of calcium into the nerve terminals, blocking fusion of neurotransmitter-containing vesicles with the synaptic membrane.[40]

These mechanisms effectively suppress neuronal firing and norepinephrine secretion

in all target effector organs containing α-2 receptors, including the central sympathetic nervous system. As a result, α-2 adrenergic agonists potently inhibit sympathoadrenal outflow, as evidenced by the decreased levels of circulating norepinephrine and the diminution of catecholamine metabolites in the urine.[41]

α-2 Agonists have been used by anesthesiologists and veterinary surgeons for the last decade as adjuncts to operative anesthesia.[42] This class of drugs, which long ago established itself as antihypertensive, has also been found to possess anxiolytic, sedative, analgesic, and antiemetic properties. These attributes make these drugs attractive in the treatment of agitation and delirium associated with catecholamine storm. α-2 agonists administered concurrently with benzodiazepines or opiate analgesics permit significantly decreased doses of these sedative-narcotics, thus minimizing side effects while maintaining effective levels of sedation and analgesia. At first, sympathetic inhibition was thought to be the major factor in decreasing anesthetic requirements when α-2 agonists were used concurrently with anesthetic agents,[43] if it was assumed that noradre- nergic neurotransmission modulates the depth of the anesthetic response.[44,45] However, subsequent studies[46] have shown that centrally active α-2 adrenergic agonists exert a powerful analgesic action by themselves, although the site and mechanism for these actions remain controversial.

The α-2 adrenergic agonist clonidine is a centrally acting antihypertensive agent reported to block the sympathetic effects of severe agitation, thus reducing the dose of sedative agents used to treat severe agitation. Among clinically available α-2 agonists, clonidine seems to be the most selective. Clonidine is thought to act by competitively binding opiate catecholaminergic receptors, thus decreasing the amount of opiates required to get the same sedative effect. As a consequence, respiratory depression, hypotension, and other side effects of narcotic sedatives are significantly attenuated, especially in hemodynamically unstable patients. Clonidine has been shown to decrease the amount of anesthesia required to obtain operative analgesia. Ghigone et al.[47] demonstrated a 45% reduction in fentanyl requirements from those in the control group of patients when clonidine at 5.0 μg/kg was administered orally before anesthesia. Clonidine has been effectively used intrathecally for analgesia in terminal cancer patients who had become tolerant to intrathecal morphine.[48,49] French investigators reported on the prolongation of spinal analgesia obtained with supplementation of bupivacaine with clonidine.[50] Clonidine has been extensively used on psychiatry wards to attenuate drug withdrawal syndrome after chronic benzodiazepine[51] and alcohol[52] use. Clonidine has also been proved to be effective in patients with panic disorders[53] as a result of its anxiolytic action and its ability to decrease the brain noradrenergic neuronal dysfunction that denominates the pathophysiology of several nonopiate withdrawal states.

Clonidine is almost completely absorbed after oral administration, but it takes 60 to 90 minutes to reach peak plasma concentration. Drug delivery through a transdermal patch takes much longer to reach effective blood levels and a minimum of 2 days to achieve a steady-state concentration.[54] Unfortunately, clonidine is not yet approved for intravenous use in the United States, but IV

administration has been investigated in Europe.[55] Postoperative patients who received after spinal fusion 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.[56] Careful titration of IV clonidine as a supplement to analgesics or sedatives in severe agitation syndromes in the 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.[57] The drug was well tolerated, with no significant related side effects.[58] In addition, dexmedetomidine has been shown to produce anxiolytic effects comparable to those of benzodiazepines, but a much less negative effect on hemodynamics.[59] Studies have shown that dexmedetomidine has no significant effect on myocardial contractile force or respiratory depression in the animal model,[60] and that α-2 agonists such as atipamezole or idazoxan could effectively reverse the hypnotic effect of the drug.[61] Clonidine was found to effectively diminish shivering as compared with droperidol or a saline control.[62]

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.[63] 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. In addition to their sedative qualities, benzodiazepines have actions that promote anxiolysis, hypnosis, anticonvulsion, and skeletal muscle relaxation. Their exact mode of action is unknown, but appears to be associated with facilitation of inhibitory gamma-aminobutyric acid (GABA–ergic) synaptic transmission throughout the brain.[64] Elderly and debilitated patients, especially those with underlying chronic obstructive pulmonary disease, are particularly at risk for hemodynamic side effects.[65] Benzodiazepines are effective as CNS depressants that decrease the perception of discomfort and the resulting anxiety. This class of drugs produce mild GABA-like effects, increasing the permeability of neuronal cell membrane to chloride ions, elevating electronegativity inside the neurons, and making them more stable in response to stimuli in the brain's reverberating circuits, thus promoting a sense of well-being. They also function as musculoskeletal relaxing agents, easing the strain of prolonged bedrest, and provide the beneficial side effect of antegrade amnesia with few negative side effects.[66]

AGITATION

Pitfalls in treatment in the ICU

Treatment of stress-induced delirium with inappropriate medications

Treating psychotic delirium with analgesic sedatives is ineffective and deceiving. These patients are usually not in pain and do not necessarily manifest excess circulating catecholamines. Therefore, the analgesic effect of morphine is lost, and the predominating effect remains that of hemodynamic and ventilatory suppression. Psychosis re-

mains in the face of compromised hemodynamics and ventilation, requiring the addition of more monitoring technology with the potential for increased stress and agitation. The treatment of psychotic delirium with CNS depressants such as benzodiazepines blurs the border between psychosis and organic brain dysfunction. Benzodiazepines have no ability to reorganize aberrant brain chemistry, and therefore psychotic patients treated with sedatives simultaneously become more obtunded and confused, which further obfuscates the treatment plan.

Treatment of pain by inappropriate medications

Attempts to avoid morphine's hemodynamic side effects by using benzodiazepines as analgesics are usually ineffective. The hemodynamic effects of benzodiazepines are small compared to those of morphine, but they do not significantly attenuate humoral responses to pain. In fact, benzodiazepines superimpose a cloud of CNS depression over pain stimuli, producing the appearance of comfort but no real analgesia. The patient may appear more comfortable but still has hypermetabolic humoral responses that continue unabated and ultimately cause end-organ damage or dysfunction. Neuroleptics such as haloperidol promote no analgesic effect and a sedative effect only in large doses, where side effects predominate. Attempts to treat agitation resulting from pain by antipsychotic neuroleptics superimpose bizarre neurologic side effects on top of pain responses. The issue may then be confused by bizarre CNS symptoms in addition to the normal humoral response of catecholamines. The patient may then feel "weird" and still in pain, and his or her agitation may increase as the patient tries to make sense of his or her distorted world.

Treatment of anxiety and discomfort with inappropriate medications

Attempts to ameliorate discomfort with analgesic sedatives such as morphine are frequently effective, but these drugs bring with them the excess baggage of hemodynamic side effects. If the patient is not really in much pain and has no attendant humoral catecholamine effects, the side effects of narcotics such as hypotension and respiratory depression predominate. Patients with compromised cardiorespiratory organs tolerate these side effects poorly and may not benefit from the analgesic effects, even in low doses. The patient may appear more comfortable but ultimately will require the application of more hardware to proctor hemodynamic side effects, thus increasing discomfort and agitation. Patients who are uncomfortable are not necessarily psychotic. The sedative actions of haloperidol are attenuated except in very large doses, at which exaggerated CNS side effects predominate. Treatment of discomfort-related agitation with antipsychotic neuroleptics usually results in bizarre CNS side effects superimposed on musculoskeletal hyperactivity. The patient may struggle more, trying to escape frightening CNS side effects. Since sedation is achieved only with large doses, extrapyramidal side effects may also be expressed.

When agitation threatens the patient

Agitation episodes that threaten hemodynamic stability are uncommon but are oc-

curring more frequently as ICUs accept wider ranges of critically ill patients for longer periods of time. Generally, such episodes are signaled by escalating agitation in the face of increasing sedative administration and by the addition of multiple drugs. Eventually, a point is reached at which the underlying causes of agitation combined with pharmacologic agent side effects threaten the patient's respiratory and hemodynamic stability. For example, the mortality of delirium tremens has been exacerbated in the past by respiratory failure brought on by the administration of sedation in the absence of adequate monitoring. Clearly, escalating magnitudes of antiagitation medications signal a serious problem that must be evaluated aggressively. A rapid evaluation of emergent medical and surgical disorders should be the first priority. This is the main reason that the patient resides in the ICU and is attached to sophisticated monitoring devices. Emergent airway decompensations can rapidly be ruled out by capnography; acute cardiac decompensations can be rapidly detected by continuous mixed venous oximetry and acute hypoxia by continuous pulse oximetry. Most of these devices come equipped with alarms that signal exceeded parameters before actual hemodynamic decompensation occurs.

Shotgun treatment plans for agitation and its attendant clinical manifestations may result in increased complications and morbidity. Inadequate or inappropriate treatment for agitation may superimpose deleterious side effects onto complications of agitation, exacerbating the symptoms and requiring further, uncomfortable monitoring devices. Hemodynamic deterioration from the effects of agitation can precipitate angina, heart failure, and cardiac arrhythmias by increasing myocardial work and oxygen consumption in the face of a fixed coronary artery output. Increased muscular activity and hypermetabolism increases CO_2 production. Patients on mechanical ventilation and chronic lung failure patients may manifest sudden increases in $PaCO_2$, which result in narcosis and obtundation or further catecholamine release, increasing agitation. Hypermetabolism at the muscular level also produces metabolic acidosis and the potential for rhabdomyolysis, myoglobinuria, and renal failure. Prolonged agitation episodes can precipitate physical injury to the patient or attending staff. Therefore, it is extremely important to search until the exact etiology of any agitation episode is identified and treated precisely.

Initial therapy for severe agitation

After emergent medical or surgical decompensations are ruled out, the somatic effects of unrelenting agitation should be quickly and effectively blunted. This will facilitate the search for the underlying etiology without concurrent end-organ impairment. The first course of action should be the administration of an IV sedative in doses titrated to obtain control of the patient with a minimum of obfuscating side effects. The ideal IV sedative drug profile should have optimal pharmacodynamic and pharmacokinetic properties (Fig 3). The short-acting benzodiazepine midazolam and the anesthetic drug propofol have many of these ideal characteristics.

Midazolam

Midazolam is a short-acting CNS depressant. An imidiazole ring is added to the benzodiazepine nucleus, which allows midazolam readily to form salts, thus increasing its

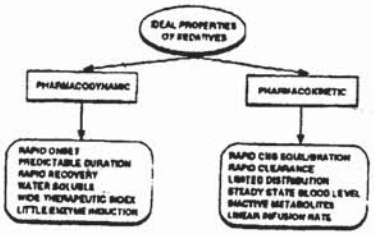

Fig 3. Ideal properties of sedatives.

solubility in aqueous solution over that of other benzodiazepines. The sedative potency of midazolam is about three to four times that of diazepam, and it has a shorter elimination half-life of 1.5 to 3.5 hours. The effect on respiratory pattern has been found to be about the same as that of diazepam in healthy subjects,[67] with approximately equal decrease in tidal volume, increase in ventilation rate, and an unaltered minute volume. Continuous titrated infusions of midazolam were found to be safe and effective compared to intermittent boluses of diazepam[68] for postoperative cardiac surgery patients, and after discontinuation of the drugs, recovery was seen to be faster in the continuous-infusion midazolam group. All of the benzodiazepines reduce the ventilatory response to hypoxia. When midazolam is administered rapidly or in large doses, its most pronounced effect is also ventilation depression. However, relatively large doses on the order of 100 to 150 µg/kg are required to produce clinically important respiratory depression.[69]

Midazolam potentiates the analgesic effect of opiates and other CNS-depressive medications, and the concurrent administration of opiates potentiates the respiratory depressive effects of midazolam. Sedation after IV injection is achieved within 1 to 5 minutes, with a duration of action of less than 2 hours. The time of onset is dependent on the total dose administered and the concurrent administration of narcotic premedication. Anterograde amnesia occurs almost immediately after IV administration and usually persists for 20 to 40 minutes after a single dose. Continuous administration of midazolam is indicated for titrated sedation, anxiolysis, and anterograde amnesia in the conscious, restless patient.[70] There is a relatively wide margin of safety when midazolam is administered by continuous infusion in the ICU setting where facilities are available for appropriate monitoring.[71] It is of the utmost importance that respiratory and hemodynamic function is monitored during the infusion of any benzodiazepine, and that the proper technology is readily available to treat sudden, unexpected decompensations.

Propofol

For extreme agitation, more potent sedation than benzodiazepines alone may be necessary. For this population of patients with life-threatening agitation syndromes, the time spent loading sedatives with variable onsets of action makes hypnotic effects erratic and unpredictable. The general anesthetic drug propofol has qualities that may make it useful as a sedative agent for severely agitated patients in the ICU. Propofol is a new IV anesthetic agent chemically unrelated to barbiturate or benzodiazepines. It produces a rapidly progressive continuum of sedation, hypnosis, and paralysis that can be maintained by continuous infusion. This spectrum of sedative activity may avoid the necessity to titrate several sedative, analge-

sic, or musculoskeletal paralytic agents all simultaneously (Fig 4).

As an IV agent for induction and maintenance of general anesthesia, propofol has been broadly reviewed in several recent publications. The cardiovascular effects of propofol are manifested as slight systemic hypotension resulting from a reduction in systemic vascular resistance.[72-74] Hypotensive episodes have been reported when propofol was administered to volume-depleted patients or when heart failure is present.[75] Cardiac index is not consistently affected when the patient is normovolemic. Minimal ventilatory depression was also observed to result from a decrease in central inspiratory drive. Sympathetic stimulation during intubation usually reverses these declines, with the net effect being a rapid return to preinduction hemodynamic status. In patients without intracranial pathology, propofol decreases cerebral blood flow and cerebral metabolic requirements for oxygen to a significant degree. This makes the application of propofol very effective in neurologic critical care for the control of elevated intracranial pressure.[76]

The most desirable features of propofol are its rapid onset of action, rapid dose titration, and rapid and clear emergence from anesthesia or sedation. The lack of accumulation allows the drug to be given by prolonged infusion. It has been compared to midazolam with regard to its effectiveness as a sedative agent[77] and was found to be remarkable because of a significantly shorter recovery time, more rapid titration efficacy, reduced posthypnotic obtundation, and faster weaning from mechanical ventilation. No accumulation was detected in a patient with severe tetanus when propofol was administered at a very high dose (20–80 mg/h) for 8 days.[78] Propofol might be appropriate as an initial agent for the induction of therapeutically induced suspended animation in syndromes that may precipitate life-threatening hemodynamic compromise (Fig 5).

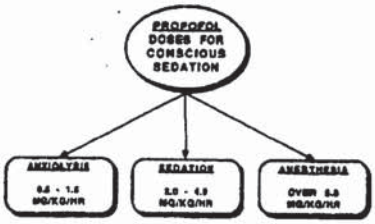

Fig 4. Doses of propofol for conscious sedation.

The role of musculoskeletal paralysis in treatment

True suspended animation can be indicated as a way to gain complete control of the situation, rather than to chance the increased hazards of partial control in unstable circum-

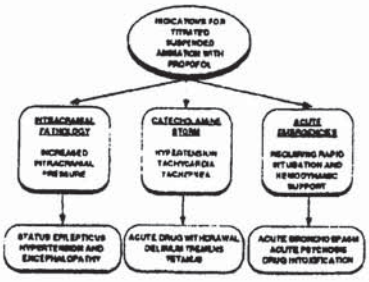

Fig 5. Indications for titrated suspended animation with propofol.

stances. The cascade of possible complications and side effects resulting from titrated suspended animation must be weighed carefully against complications resulting from the agitation episode itself. If agitation becomes so severe that hemodynamic stability is threatened, endotracheal intubation and mechanical ventilation may be necessary to prevent cardiorespiratory collapse.[79] The option of placing a patient in suspended animation by musculoskeletal paralysis for severe, unrelenting agitation should be approached with caution. For example, a "chicken-or-egg" paradox regarding blood oxygenation must be resolved quickly and effectively. If the patient's agitation results from hypoxia and hypercarbia, establishment of an airway and ventilation will rapidly correct the situation. But, if the patient is hypoxic and hypercarbic because of agitation, intubation and ventilation will only make him or her more agitated.[80-82]

Suspended animation by musculoskeletal paralytic agents will effectively stop the effects of muscular hyperactivity on end-organs, but the causation still must eventually be found. The humoral effects of catecholamine release may alone be enough to cause ongoing end-organ damage. Therapeutic musculoskeletal paralysis should be considered when sedative side effects begin to pose a risk to hemodynamics and respiratory function and the patient is still not controlled. In these situations, escalating doses of sedatives threaten sudden and unpredictable compromise to cardiac, pulmonary, and hemodynamic function. If the situation reaches this stage, it is better to remove unpredictable factors and gain control of the situation by placing the patient's hemodynamics in suspended animation while pathologic causes are investigated. Patients can be paralyzed quickly with an appropriate dose of vecuronium, with minimal histamine release that might cause vasodilatation and hypotension.[82] They can then be intubated and placed on mechanical ventilation, which effectively stops deleterious effects on end-organs.

SEDATION

The therapeutically paralyzed patient

Intentional therapeutic paralysis may be complete or attenuated, allowing the patient some movement but not unrestrained activity. Doses of vecuronium may effectively be guided by peripheral nerve stimulators according to protocols described elsewhere. However, it must be remembered that underneath paralysis lies unprotected cerebral function. It is absolutely mandatory that sedation and hypnosis be tailored to ameliorate the helpless feeling of paralysis in the awake state, a "buried-alive" feeling.[83] Since musculoskeletal paralysis does not attenuate the effects of catecholamine release, sedation has in the past been titrated under paralysis until tachycardia and hypertension normalize, which suggests that patient comfort has been achieved. This is a rough way of determining patient comfort under the effects of paralysis, but the advent of cerebral function monitoring has dramatically improved on this method.

Cerebral function monitoring for sedated patients

Modern cerebral function monitors survey brain electrical activity in real-time and re-

flect changes in brain activity caused by sedatives. Agitation is represented by linear activity depicting the intensity of brain activity and the position of the activity within the brain topography. Sedation can be effectively titrated until this activity is reduced to normalcy by using continuous infusion of sedative agents, which ensures patient comfort under paralysis while the search for underlying pathology follows. Different classifications and combinations of sedatives, analgesics, and antipsychotics can be tried until the combination that brings about the most appropriately calm cerebral function tracing is discovered. Attention can then be turned to protecting other end-organs from damage.

In the ICU, a brain activity monitor (Life scan, Neurometrics, San Diego, California) allows monitoring of the quantity and geography of brain electrical activity in real-time, thus providing important information regarding adequacy of sedation. The monitor displays cerebral electrical activity by processing the electroencephalogram (EEG) signal through a periodic analysis as a three-dimensional moving picture in two "glass boxes" corresponding to the right and left hemispheres (Fig 6). Aperiodic analysis is a real-time processing technique that continually transforms raw EEG information from both hemispheres into frequency and amplitude. Within each box, waves are depicted as "vectors," with the height and position of each showing its amplitude and frequency, respectively. Frequency bands are displayed in the horizontal position, by color, with lower frequencies (0.5 Hz) to the left and higher frequencies (30 Hz) to the right. The frequency of each wave can be determined by the color band in which the pole appears: Delta, 0.5–3 Hz, dark blue; Theta, 3–7 Hz, light blue; Sub-Alpha, 7–9 Hz, magenta; Alpha, 9–12 Hz, green; and Beta, 12–30 Hz, yellow.

The amplitude is reflected by the altitude of the electrical spikes. Depending on the selected display type, the height of the pole either displays the amplitude of each wave (Display type A) or is proportional to all activity within that frequency (Display type B). The amplitude range can be set to view brain activity at 50, 100, 200, or 400 μv of wave height, depending on the energy of the voltage activity of brain electrical activity. Lesser voltages are more sensitive and are used to display cerebral activity when brain activity is quiescent. Real-time brain electrical activity is recorded in time increments selected by the viewer and can be recalled for comparison. The activity edge is a white line that

Fig 6. Brain activity monitor.

lies above the glass box and is a gross summation of changes in both frequency and amplitude. It helps to identify the general trend in cerebral electrical activity and serves as a "single-number" indicator that provides a quick, generalized indication of brain activity for each cerebral hemisphere.

A technique has been developed to simplify the pattern recognition and interpretation of the brain electrical activity using the key word SAFE, taken from the first letter of the terms for its four components: 1) Symmetry: Compare the pattern of the left hemisphere with that of the right hemisphere. Asymmetrical patterns can indicate diminished perfusion to one hemisphere, cerebral embolism, or thrombosis. 2) Amplitude: Compare the altitude of the vectors. Asymmetric hemispherical amplitude variations may suggest seizures. Symmetrically increased altitudes suggest agitation under paralysis. Low amplitude suggests adequate sedation and quiescence. 3) Frequency: Compare the distribution of vectors throughout all frequency bands. Higher altitudes in the light-colored bands suggest conscious brain activity and darker colors suggest activity in the deep centers of the brain, possibly sympathetic hyperactivity. Absent or attenuated activity in the "conscious" side suggests anesthesia. Hypertension and tachycardia are frequently associated with increased activity on the dark "unconscious" side. 4) Edge: Observe the activity edge. Significant dips in one hemisphere compared to the other suggest focal brain ischemia.

The following conditions in therapeutically paralyzed ICU patients may be accurately monitored by the Lifescan monitor

Especially under therapeutic paralysis, inadequacy of sedation is manifested by a diffuse, symmetrical increase in amplitude throughout the entire frequency range representing hyperactive brain activity (Fig 7).

With adequacy of sedation, sedatives and anxiolytics decrease brain electrical activity (Fig 8). Narcotics and benzodiazepines generally exhibit a gradual reduction in activity at higher frequencies (conscious side) and increased activity at lower frequencies (unconscious side). The activity edges symmetrically shift to the left. The amplitude of the deep center delta waves may increase, which suggests increased sympathetic activity. Barbiturates at low to moderate doses reduce alpha and beta activity (conscious side) and

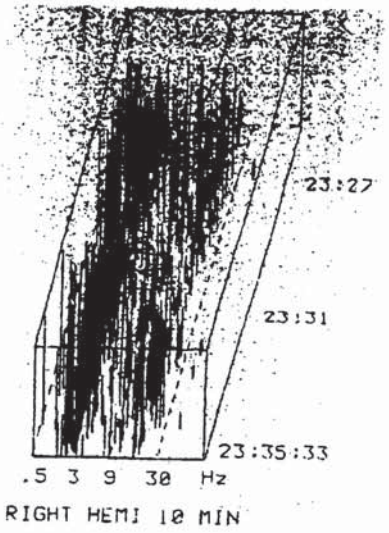

Fig 7. Inadequacy of sedation results in hyperactive brain activity.

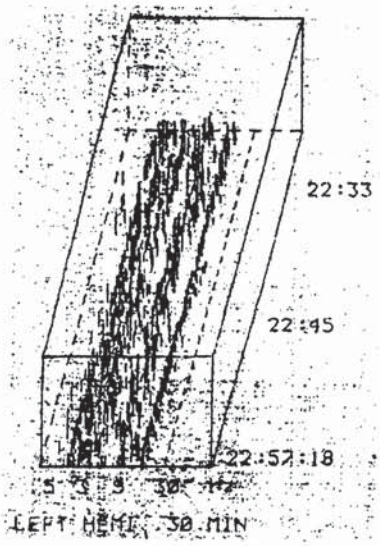

Fig 8. Adequate sedation decreases brain electrical activity.

increase the amplitude and activity in (unconscious side) delta/theta activity. Large barbiturate doses suppress all brain activity, resulting in a "flat" screen.

Hypoxia is generally seen as a shift to the left of the activity edge, a reduction in activity at all frequencies, and especially a decrease in amplitude at higher frequencies.

The Lifescan monitor is not designed to replace a more sophisticated multiple-electrode diagnostic EEG, but is designed to make real-time brain electrical activity information readily accessible in the ICU. In the critical care setting, this monitor can assist in observing changes in cerebral perfusion, estimating and controlling depth of sedation, and monitoring for seizure activity.

PROTECTION OF END-ORGANS FROM METABOLIC STORM—TITRATED SUSPENDED ANIMATION

Once the patient is placed in suspended animation, many end-organs can be protected while specific therapeutics or the mere "tincture of time" resolves the fundamental causes of the agitation syndrome. The adverse effects of exogenous catecholamines and endogenous neurotransmitters on the brain can be blunted by titrating sedative, hypnotic, and analgesic drugs to levels of cerebral electrical activity as monitored by cerebral function monitors in real-time. Catecholamine storm and severe tachycardia cause a dramatic increase in myocardial oxygen consumption, which can lead to severe cardiac and hemodynamic complications. Several intravenous beta-adrenergic antagonists are available for use in the ICU. Atenolol is relatively water-soluble, incompletely absorbed, and cleared by the renal route and has a fairly long half-life. Metoprolol is highly lipid-soluble, is more completely absorbed, is cleared by the hepatic route, and has a relatively short half-life. Esmolol, a short-acting, rapidly titratable β-adrenergic blocking agent, has been demonstrated to manifest a preferentially negative chronotropic effect and can be titrated by continuous infusion.[84] The effects of hypertension with concomitant tachcardia can be safely resolved by using titrated IV infusions of labetalol, a drug manifesting both α- and β-adrenergic antagonistic properties.[85] Labetalol can also be used as a continuous infu-

sion, titrated in relatively brief intervals.[86] Cardiac function and fluid volume status can be monitored accurately by a pulmonary artery catheter and continuous mixed venous oximetry, free from variations induced by patient movement. Once the agitation syndrome runs its course, hemodynamic and cerebral parameters will begin to normalize, and the patient can be deintensified safely.

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REVIEW

Benzodiazepine sedation and the use of benzodiazepine antagonists in intensive care

Michael L Pepperman

Sedation of critically ill patients in an intensive care unit is a complex issue. Multiple factors influence the response of individual patients to specific drugs. Over the past few years, the benzodiazepines have proven safe and effective sedative agents for patients in this environment. The introduction of a specific benzodiazepine antagonist, flumazenil, now gives the clinician an opportunity rapidly to reverse, either temporarily or permanently, the central depressant effects of the benzodiazepines.

Benzodiazepines were first introduced in 1960 when chlordiazepoxide librium was released. Since then they have been widely used in medical practice because of their anxiolytic, sedative, hypnotic, anticonvulsant, amnesic and muscle relaxant properties.

The benzodiazepines exert their depressant effect on neuronal activity by selective enhancement of inhibitory GABAergic synaptic transmissions to most parts of the central nervous system,[1-3] following interaction between the benzodiazepine and specific neuronal membrane receptors.[3,4] Gamma-aminobutyric aid (GABA) is the most important inhibitory neurotransmitter in the central nervous system.

The administration of benzodiazepines leads to a graded response with lower doses resulting in a relief of anxiety, whilst higher doses are associated with muscle relaxation and hypnosis (Table 1).

There are many factors that will influence the response in an individual patient to the administration of a sedative agent such as a benzodiazepine (Table 2). In establishing a sedative regimen the clinician must therefore assess each patient carefully before choosing the sedative agent, dose and route of administration appropriate to the patient. A constant reappraisal of a sedative regimen is required if the desired level of sedation is to be maintained throughout the treatment period. The risks of an iatrogenic overdose and the problems associated with a prolonged half life of the sedative agent can be reduced, if not avoided.

The benzodiazepines often have a longer duration of action than is clinically necessary resulting in a slower recovery than desirable after the administration of the benzodiazepine has been stopped. The problem is compounded by the fact that most of the benzodiazepines have active metabolites.

The introduction of midazolam in 1982 has improved the situation in that it has a shorter elimination half life

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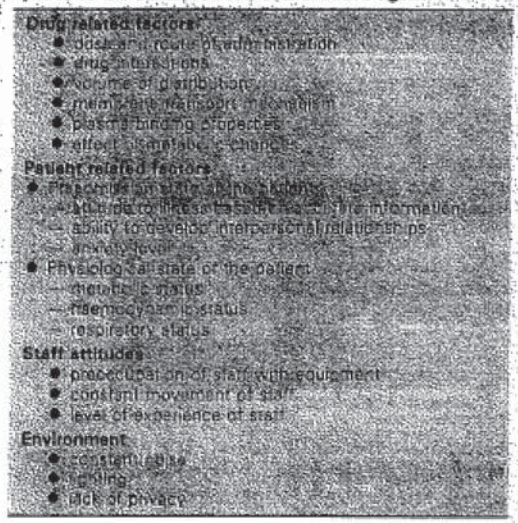
Table 1. Graded responses associated with the administration of benzodiazepines and flumazenil

Table 2. Factors that influence the individual patient response to the administration of a sedative agent



(approximately 90 minutes) and the primary metabolite, hydroxymidazolam, is pharmacologically less active, with a shorter elimination half life than midazolam.[5]

The identification of specific benzodiazepine receptors in 1977 stimulated research to identify a specific benzodiazepine antagonist. A number of imidazodiazepines were synthesised. The majority, whilst showing a high *in vitro* affinity for the benzodiazepine receptor, only had a weak *in vivo* pharmacological activity. Several compounds, however, had antagonistic properties and one, flumazenil, was found to be a specific benzodiazepine antagonist with minimal intrinsic activity. Flumazenil was first characterised in 1979 and is a potent competitive inhibitor of the specific binding of the benzodiazepines at the receptor.[6] Clinical trials related to the use of flumazenil started in 1986 and have demonstrated the efficacy of the drug in reversing the effects of benzodiazepines when used as a supplement during general anaesthesia,[7] as a supplement to local or regional anaesthesia,[8,9] and after the longer term use for intensive care sedation.[10,11]

Flumazenil is tolerated well and has minimal intrinsic effect (partial agonist activity). In healthy volunteers, flumazenil has an elimination half life of approximately 60 minutes.[12,13] There is a minimal risk from therapeutic, intentional or accidental overdose.[14]

Benzodiazepine sedation in intensive care

Intensive care medicine is a relatively new branch of medicine that has developed rapidly over the past 25 years. The accepted role of an intensive care unit (ICU) is the management of patients with life threatening conditions requiring:

- intensive monitoring;
- continuous reassessment of therapeutic regimens;
- the application of special techniques.

The type of patient admitted to intensive care facilities varies tremendously, most units dealing with a broad spectrum of patients, both in respect of age and pathology. Thus, the concept of sedation for patients receiving treatment in an ICU is a very complex issue. It is unrealistic to consider the possibility of a single regimen for sedation as being satisfactory in all situations.

Most clinicians consider themselves experts in the field of sedation but it remains a Cinderella subject. We have little knowledge of the benefits of sedation to an individual patient. At times it would appear that sedation is used primarily to benefit the medical staff rather than the patient.

The heavy anaesthetic input in intensive care medicine in the United Kingdom has resulted in sedative regimens being an extension of anaesthetic practices. As a result, most anaesthetic agents have been used as sedative agents for intensive care patients. The majority are no longer used because of the recognition of undesirable side effects. Initial experiences with etomidate and althesin (Alphaxalone and Alphadalone) administered by continuous intravenous infusion to provide sedation in the intensive care patient proved successful. However, observations regarding increased mortality associated with a significant decrease in adrenocortical function in patients sedated with etomidate[15,16,17] and an undesirable effect on serum albumin in patients sedated with althesin[18] led to both agents being withdrawn from use.

The word sedation is derived from the Latin *sedone* which means to soothe or to settle. Current concepts as to what represents an ideal level of sedation are compatible with this definition of sedation in that the aim is to have a patient who is co-operative, orientated and tranquil when aroused but who will sleep when not disturbed.[19] It has been suggested that the ideal sedative agent should have the following profile:

- should have no effect on the cardiovascular or respiratory systems;
- should have no effect on the metabolism of other drugs;
- should be metabolised by pathways not dependent on normal renal or hepatic function;
- should have a short elimination half life.

At present there is no agent available which totally fits this profile. In choosing a sedative agent for an intensive care patient the clinician must consider the clinical requirements (Table 3).

A survey of sedative practices in 189 ICUs in the United Kingdom showed that in 60% of the units a combination of a benzodiazepine and an opiate had become the standard sedative regimen.[20] As the benzodiazepines have no specific analgesic properties, the need for adequate analgesic cover when sedating patients with these agents is a vital consideration.

As highlighted previously, the problem with the benzodiazepines is the potentially long elimination half life. There are many factors influencing the duration of action of sedative agents (Table 2). Since the introduction of the benzodiazepines there have been many reports of a prolonged duration of action in patients with impaired hepatic function[21,22] and septic shock.[23] Dundee *et al* suggest that about 6% of the population are also poor metabolisers of the benzodiazepines.[24]

Diazepam was the most commonly used benzodiazepine in intensive care prior to the introduction of midazolam. Diazepam has an elimination half life of 24–72 hours in healthy subjects and has two active metabolites, desmethyldiazepam and oxazepam, the former having a longer elimination half life than diazepam.[25] The introduction of midazolam with a rapid onset, an elimination half life of 90 minutes,[26] and metabolites with a much shorter elimination half life has improved the situation. However, even an elimination half life of 90 minutes may still be inappropriate as it detracts from:

- the ability to assess the patient;
- delay in weaning off ventilators;
- in self-ventilating patients the potential to maintain an adequate level of respiratory function.

The introduction of flumazenil as a specific benzodiazepine antagonist has enabled the central depressant effects of benzodiazepines to be reversed rapidly after the administration of the benzodiazepine has been stopped.

The duration of action of flumazenil is dictated by several factors, chief of which are:

- the dose of flumazenil;

- the time elapsed since the benzodiazepine antagonist was given;
- the total dose and elimination half life of the benzodiazepine agonist given.

The many factors that can lead to a significant prolongation of the central nervous system depression associated with the use of benzodiazepines have been highlighted and often a single intravenous dose of flumazenil leads only to a temporary reversal of the central effects of the benzodiazepine for 20–45 minutes after which resedation may occur.

Reversal of long term benzodiazepine sedation

Temporary interruption. It is often advantageous to be able to assess the clinical status of the ICU patient periodically. The administration of a single intravenous bolus of 200 mcg of flumazenil given slowly over 15–30 seconds is usually sufficient to reverse the central depressant effect of a benzodiazepine giving a therapeutic window of 20–40 minutes during which time a full neurological and clinical assessment can be carried out.

If the flumazenil is titrated in slowly against the response then concerns about precipitating an acute anxiety state can be minimised, especially if the patient is handled correctly by the medical and nursing staff during the transitional phase. The specificity of flumazenil ensures that the effect of analgesics remains the same. A slight rise in blood pressure and pulse rate may be seen to be associated with the decrease in sedation.

This therapeutic window can prove beneficial not only in allowing for a reappraisal of therapeutic regimens but also may help in diagnosis when causes of a semi-conscious or sedated state other than the use of benzodiazepines may be present. If the administration of flumazenil reverses the central depressant effects the possibility of other causes can be excluded.[27]

The short elimination half life of flumazenil allows for easy resedation with a benzodiazepine if appropriate.

Permanent reversal. Several clinical trials have demonstrated the efficacy of flumazenil in reversing the central depressant effects of the benzodiazepines after their long term use for intensive care sedation.[10,11]

The long term use of benzodiazepines by either repeated intravenous bolus administration or by continuous intravenous infusion in the seriously ill patient can lead to a significant accumulation of the agent and a prolonged elimination half life.[25,29] The short elimination half life of flumazenil means that repeated bolus doses or a continuous infusion of the antagonist may be required to prevent resedation. If repeated bolus doses are used then after the initial slow intravenous administration of 200 mcg further doses of 100 mcg should be administered at one minute intervals until the desired level of consciousness is obtained and maintained.[11] Alternatively, the antagonist can be administered by a continuous intravenous infusion.[16] An initial slow intravenous infusion of 200 mcg will normally result in a return to a desired level of consciousness and then an infusion of between 100 and 200 mcg per hour can be titrated against response to maintain the situation.

Table 3. Clinical requirements that have to be considered when choosing a sedative agent

The recommended maximum total dose of flumazenil when used to reverse the central effects of a benzodiazepine in an ICU is 2 mg. As it is now common practice in ICUs to administer drugs by continuous intravenous infusions, it would seem logical to administer flumazenil this way. The risk of precipitating an acute anxiety state can be reduced to a minimum by ensuring that the rate of infusion of the first 200 mcg is slow enough to allow for a slow transition from the sedated to the aroused state. If the benzodiazepine used for sedation is midazolam and the sedative regimen was regulated properly to maintain the desired level of sedation, then the infusion of flumazenil can be stopped in the majority of patients after three hours without the risk of resedation. However, a small number of patients may resedate and need further increments of flumazenil if this is deemed appropriate.[28]

Weaning from mechanical ventilation. Benzodiazepines used to sedate patients satisfactorily in intensive care not only have a central depressant effect diminishing central respiratory drive but also diminish the strength of the respiratory muscles, thus potentially making weaning more difficult. In reversing all the central effects of the benzodiazepines, flumazenil leaves a more responsive and co-operative patient with a more effective central respiratory drive and more strength in his respiratory muscles. These improvements facilitate the return to spontaneous respiration and possible weaning from the ventilator much earlier than would be expected in patients sedated for some time with a benzodiazepine. This may permit extubation of the patient.

Benzodiazepine overdose. Flumazenil has proven effective in reversing the central depressant effects of benzodiazepines in those patients who present with a history of a benzodiazepine overdose caused by either an accidental or an intentional misuse of the drug.[30,31]

If the patient presents with a pure benzodiazepine overdose then flumazenil will reverse the central depressant effects within five minutes. In the intentional overdose, however, the benzodiazepine is often only one of the drug types taken. In this situation, the administration of flumazenil may only lead to a partial improvement in the level of consciousness and respiratory function rather than total recovery. The titration of a bolus of 100–200 mcg of flumazenil therefore may prove helpful in both the diagnostic and therapeutic areas in these cases. It will confirm the presence of sedation related to the effects of a benzodiazepine by reversing any central depressant effects related to its presence. Further doses of flumazenil can be given if it is considered desirable.

An improvement in the level of consciousness and respiratory function in either group, the accidental or intentional overdose patient, may reduce if not prevent the need to intubate and/or ventilate the patient whilst allowing for the safe introduction of standard therapeutic regimens. The need for careful observation and monitoring of these patients is not reduced: however; this can often be related to their care in a ward rather than an intensive care environment.

In multiple overdose situations there is always the problem that the central effects of the benzodiazepines may be suppressing the potentially damaging effects associated with the overdose of other drugs taken at the same time. The tricyclic antidepressants may precipitate convulsions if the drug is taken in excess, convulsions that would be suppressed if not prevented by the presence of a benzodiazepine. If the benefits of reversing the central effects associated with the presence of a benzodiazepine outweigh the potential risks of doing this in an individual patient, then it is essential that the initial dose of flumazenil is small and is titrated in slowly. If any undesirable problems develop (convulsions) then no further flumazenil should be given. The short elimination half life of flumazenil allows for the early administration of a benzodiazepine such as midazolam to resedate the patient if this is desirable.

At present, flumazenil is not licensed in the UK for use in the treatment of benzodiazepine overdoses but there may well be a place for its use in a controlled environment by suitably qualified individuals in support of an active management regimen, especially in trying to reverse the depression of respiratory function associated with benzodiazepine sedation.

Conclusion

The benzodiazepines have proved to be safe and effective sedative agents for patients in an intensive care environment. The wide variety of patients admitted to most ICUs is associated with an individual variability in patient responses to these drugs which, in some cases, may be detrimental to their progressive management. The effect of the benzodiazepine may be unexpectedly intense or the recovery may be unacceptably long. The need periodically to assess the clinical status of patients is also advantageous and often requires temporary reversal of sedation. The introduction of flumazenil as a specific benzodiazepine antagonist provides the clinician with a safe and effective method of reversing the central depressant effects of the benzodiazepines, either temporarily or permanently, whenever this is indicated. □

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

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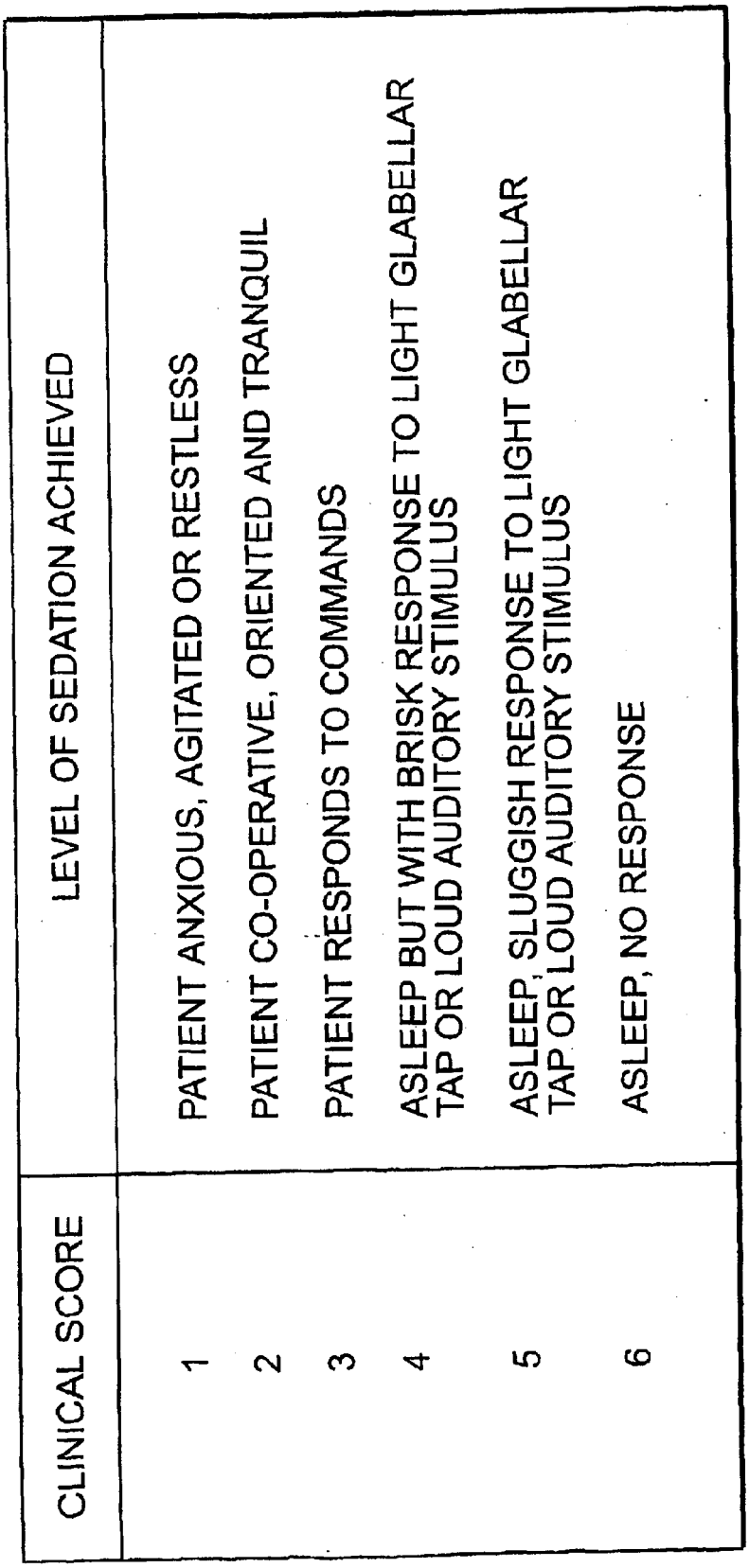
(57) **ABSTRACT**

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

12 Claims, 2 Drawing Sheets



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

FIG. 1

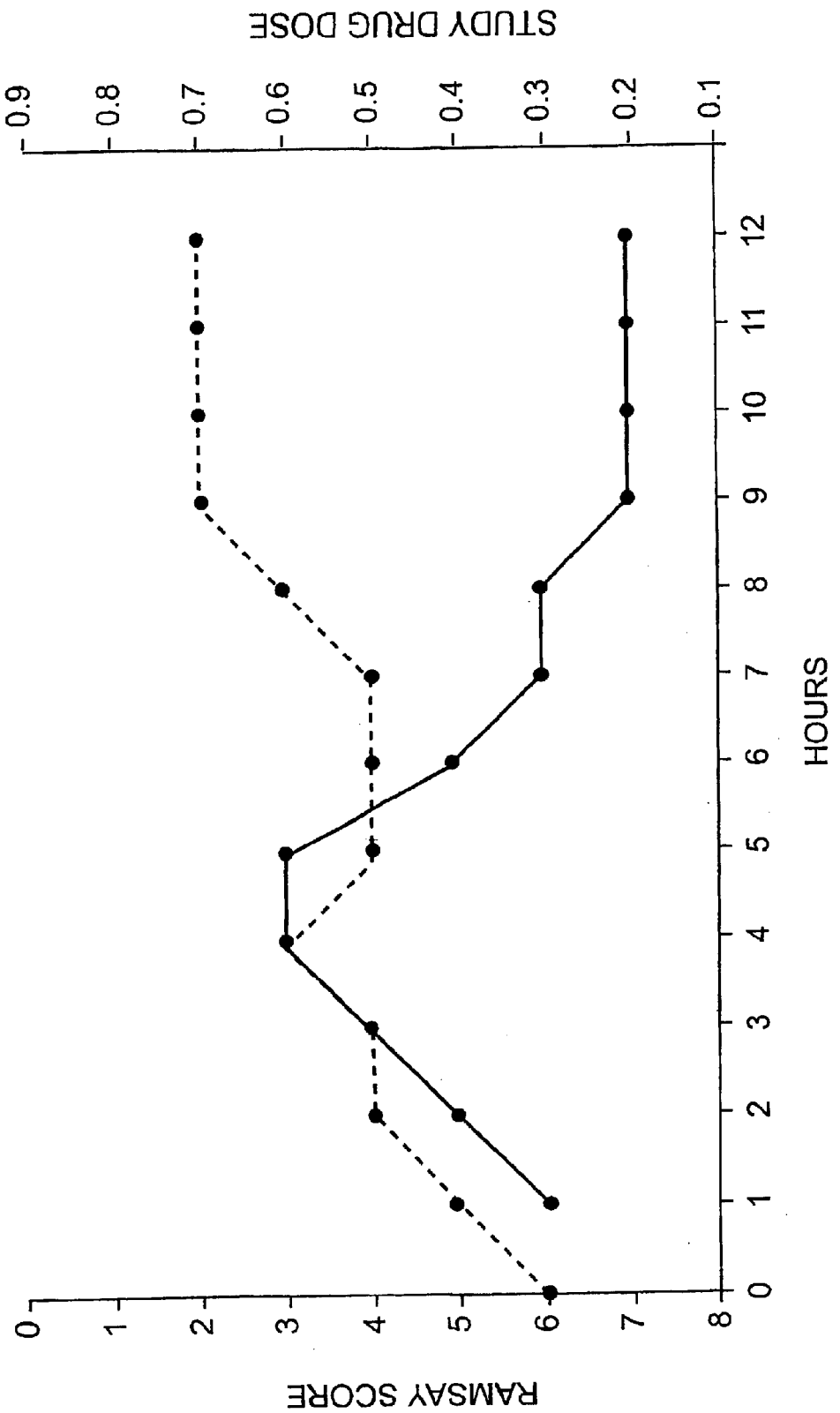

STUDY DRUG DOSE
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
5
6
7
8
9
10
11
12
HOURS
RAMSAY SCORE
0
1
2
3
4
5
6
7
8

FIG. 2

USE OF DEXMEDETOMIDINE FOR ICU SEDATION

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

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

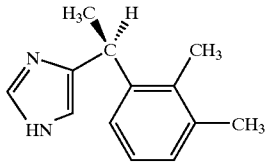
α_2-adrenoceptor agonists are being evaluated in general anaesthetic practice because of their sympatholytic, sedative, anaesthetic, and hemodynamic stabilizing effects. Tryba et al. discussed the usefulness of α_2-agonists in situations where patients with withdrawal symptoms are treated in the ICU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

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

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

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

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



Dexmedetomidine is described in U.S. Pat. No. 4,910,214 as an α_2-receptor agonist for general sedation/analgesia and the treatment of hypertension or anxiety. U.S. Pat. Nos. 5,344,840 and 5,091,402 discuss dexmedetomidine in perioperative and epidural use, respectively. U.S. Pat. No. 5,304,569 discusses the use of dexmedetomidine in glaucoma. U.S. Pat. No. 5,712,301 discusses the use of dexmedetomidine for preventing neurodegeneration caused by ethanol consumption.

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

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

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

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

The chemical form for dexynedetomidine can be the free base or an acid addition salt. Such acid addition salts may be formed, for example, with inorganic acids, such as, hydrochloric acid, hydrobromic acid, sulfiric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

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

EXAMPLE 1

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

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

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

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

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

EXAMPLE 2

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

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

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

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

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

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

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

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

EXAMPLE 3

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

What is claimed is:

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

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

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

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

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

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

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

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

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

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

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

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

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,716,867 B1
DATED : April 6, 2004
INVENTOR(S) : Riku Aantaa et al.

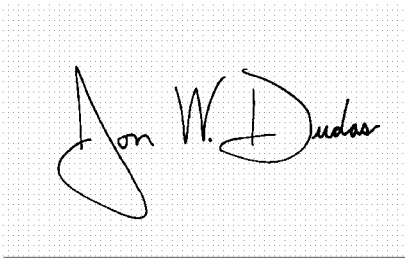
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [57], **ABSTRACT**,
Line 3, "of a" should read -- or a --.
Item [73], Assignee, add second assignee -- **Abbott Laboratories**, Abbott Park, IL (US) --

Column 14,
Line 15, "dexmedetomidine of" should read -- dexmedetomidine or --.
Line 26, "ane" should read -- and --.
Line 29, "pharmaceutically" should read -- or pharmaceutically --.

Signed and Sealed this

Twenty-fifth Day of May, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office