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Dexmedetomidine

A Review of its Use for Sedation in Mechanically Ventilated Patients in an Intensive Care Setting and for Procedural Sedation

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Data Selection

Sources: Medical literature (including published and unpublished data) on 'dexmedetomidine' was identified by searching databases since 1996 (including MEDLINE and EMBASE and in-house AdisBase), bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'dexmedetomidine' and 'sedation'. Searches were last updated 25 July 2011.

Selection: Studies in initially intubated and mechanically ventilated patients in an intensive care setting and in non-intubated patients prior to and/or during surgical and other procedures who received dexmedetomidine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Dexmedetomidine, pharmacodynamics, pharmacokinetics, sedation, therapeutic use, tolerability.

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Abstract

Dexmedetomidine (Precedex®), a pharmacologically active dextroisomer of medetomidine, is a selective α_2-adrenergic receptor agonist. It is indicated in the US for the sedation of mechanically ventilated adult patients in an intensive care setting and in non-intubated adult patients prior to and/or during surgical and other procedures. This article reviews the pharmacological properties, therapeutic efficacy and tolerability of dexmedetomidine in randomized, double-blind, placebo-controlled, multicentre studies in these indications.

Post-surgical patients in an intensive care setting receiving dexmedetomidine required less rescue sedation with intravenous propofol or intravenous midazolam to achieve and/or maintain optimal sedation during the assisted ventilation period than placebo recipients, according to two randomized, double-blind, multinational studies. Moreover, significantly more dexmedetomidine than placebo recipients acquired and/or maintained optimal sedation without rescue sedation. Sedation with dexmedetomidine was also effective in terms of the total dose of morphine administered, with dexmedetomidine recipients requiring less morphine than placebo recipients; with regard to patient management, dexmedetomidine recipients were calmer and easier to arouse and manage than placebo recipients.

Intravenous dexmedetomidine was effective as a primary sedative in two randomized, double-blind, placebo-controlled, multicentre studies in adult patients undergoing awake fibre-optic intubation or a variety of diagnostic or surgical procedures requiring monitored anaesthesia care. In one study, significantly fewer dexmedetomidine than placebo recipients required rescue sedation with intravenous midazolam to achieve and/or maintain optimal sedation; conversely, in another study, rescue sedation with intravenous midazolam was not required by significantly more dexmedetomidine than placebo recipients. Primary sedation with intravenous dexmedetomidine was also effective in terms of the secondary efficacy endpoints, including the mean total dose of midazolam and fentanyl administered and the percentage of patients requiring further sedation (in addition to dexmedetomidine or placebo and midazolam), with, for the most part, significant between-group differences observed in favour of dexmedetomidine over placebo. In general, no significant differences were observed between the dexmedetomidine and placebo treatment groups in the anaesthesiologists' assessment of ease of intubation, haemodynamic stability, patient cooperation and/or respiratory stability.

Intravenous dexmedetomidine is generally well tolerated when utilized in mechanically ventilated patients in an intensive care setting and for procedural sedation in non-intubated patients. Dexmedetomidine is associated with a lower rate of postoperative delirium than midazolam or propofol; it is not associated with respiratory depression. While dexmedetomidine is associated with hypotension and bradycardia, both usually resolve without intervention.

Thus, intravenous dexmedetomidine provides a further option as a short-term (<24 hours) primary sedative in mechanically ventilated adult patients in an intensive care setting and in non-intubated adult patients prior to and/or during surgical and other procedures.

1. Introduction

Sedation comprises a continuum of four states: minimal sedation (anxiolysis); moderate sedation/analgesia (conscious sedation); deep sedation/analgesia; and general anaesthesia.[1] By engendering a suppressed level of consciousness, sedation enables a patient to endure a painful or unpleasant

diagnostic or therapeutic procedure by minimizing awareness, discomfort and memory, while endeavouring to preserve spontaneous respiration and airway-protective reflexes.[1,2] Intravenous sedation is thus considered integral in patients in an intensive care setting, particularly those requiring mechanical ventilation,[3] with its utilization for interventional procedures in a number of settings, including endoscopic procedures, becoming more widespread.[4]

Dexmedetomidine (Precedex®) is an α_2-adrenergic receptor agonist that acts via a receptor distinct from the γ-aminobutyric receptor utilized by benzodiazepines and propofol.[5] The utilization of intravenous dexmedetomidine as a sedative in post-surgical patients in an intensive care setting has been reviewed previously.[6] This article reviews the pharmacological properties, therapeutic efficacy and tolerability of dexmedetomidine in the sedation of mechanically ventilated patients in an intensive care setting (when administered for up to 24 hours) and in procedural sedation. Given that dexmedetomidine is not indicated for infusions longer than 24 hours in duration,[7] studies in which dexmedetomidine was administered for more than 24 hours are beyond the scope of this review.

2. Pharmacodynamic Properties

The pharmacodynamic properties of dexmedetomidine are well established and have been reviewed previously.[6] Therefore, a brief overview is presented in the following section and summarized in table I.

Dexmedetomidine, a pharmacologically active dextroisomer of medetomidine, is a selective α_2-adrenergic receptor agonist.[7-9] It binds to transmembrane G protein-binding adrenoreceptors in the periphery (α_{2A}-adrenoceptor subtype) and in the brain and spinal cord (α_{2B}- and α_{2C}-adrenoceptor subtypes),[8] with a dose-dependent α_2-selectivity that is approximately 7- to 8-fold greater than that of clonidine.[9,10] In animals, α_2-selectivity was observed following the slow intravenous infusion of low and medium doses of dexmedetomidine (10–300 μg/kg), while both α_1- and α_2-activity was observed following the slow intravenous infusion of high doses of dexmedetomidine (≥1000 μg/kg) or following rapid intravenous administration.[7] Dexmedetomidine also binds to imidazoline receptors, potentially explaining the non-α_2-adrenoreceptor-related effects of α_2-adrenergic receptor agonists.[11]

α_2-Adrenergic receptor agonists such as dexmedetomidine generate, among other effects, sedation and sympatholysis, as well as having opioid-sparing properties.[10] Stimulation of the α_2-adrenoceptor subtypes mediates sedative and antinociceptive actions (α_{2A}) and a vasoconstrictive cardiovascular effect (α_{2B}), and modulates dopaminergic neurotransmission, hypothermia and a variety of behavioural responses (α_{2C}).[12] In addition, α-adrenergic receptor agonists activate potassium ion channels, ultimately resulting in the suppression of neuronal activity.[12] The consequence of this is an inhibition of noradrenaline (norepinephrine) release, engendering a reduction of excitation, especially in the locus coeruleus.[12] The locus coeruleus is the major site of noradrenergic innervations in the brain,[13] and has also been implicated as a key modulator in a variety of α_2-adrenergic receptor agonist-directed brain functions, including anxiety, arousal, sleep and the withdrawal associated with CNS depressants (e.g. opioids).[12]

The effects of dexmedetomidine on haemodynamics (e.g. blood pressure [BP] and heart rate [HR]) are as expected for an α_2-adrenergic receptor agonist; bradycardia and hypotension are among the most commonly reported adverse events in patients receiving dexmedetomidine (section 5).[41-43] For instance, in a study in post-surgical patients in an intensive care setting (see section 4 for study design and full treatment regimen details), BP and HR values for most dexmedetomidine recipients were reported as remaining within clinically acceptable ranges.[41]

The mean changes from baseline in systolic BP (SBP) were on average approximately 7 mmHg lower in dexmedetomidine than in placebo recipients during infusion, with significant between-group differences observed from 20 minutes to 1 hour and from 4 to 20 hours following the initiation of the study medication.[41] However, there was no significant between-group difference in the variability of actual SBP values.[41]

Table I. Summary of the main pharmacodynamic properties of dexmedetomidine. Data are derived from studies in healthy volunteers[a][14-22] and patients (pts),[b][23-40] and from the US prescribing information[7]

Sedative effects (see section 4)
Induces dose-related sedation[14]a
Induces a form of sedation resembling natural sleep from which the pt is easily and quickly aroused[15,27,31]a,b
Opioid-sparing/analgesic effects (see section 4)
Induces dose-related analgesia in healthy volunteers[14]
Reduces, but does not replace, requirements for opioids and other analgesics[16-18,27,28]a,b
Prolongs sensory and/or motor blocks induced by bupivacaine spinal[37,38] or epidural[30] analgesia[b]
Prolongs the duration of the brachial plexus blocks[40]b and the spinal anaesthetic action of prilocaine[29]b
Haemodynamic effects
Demonstrates a biphasic effect on BP.[19]a Transient elevations observed with high doses (e.g. during the loading dose) as a result of peripheral vasoconstriction, followed by reductions in BP owing to central and peripheral sympatholytic effects.[7,19]a At lower doses, reductions in BP are observed[19,24,36]a,b
Has the potential for pronounced hypotension in pts with pre-existing hypovolaemia[7]
Reduces heart rate,[14,24,25,36]a,b even at low doses[25]b
Associated with clinically significant bradycardia and sinus arrest in young, healthy volunteers with high vagal tone or with different routes of administration, including bolus or rapid intravenous administration[7]
Prolongs the QT interval and shortens the corrected QT interval[34,35]b
Reduces cerebral blood flow[20] in a dose-related manner[21]a
Respiratory effects
Has minimal effects on respiratory function,[14,24,36,39]a,b with the respiratory rate and oxygen saturation remaining within normal limits and no evidence of respiratory depression[7,36]a,b
Metabolic effects
Reduces cerebral metabolic rate in a dose-related manner[21]a
Associated with reduced shivering[26]b
Endocrine effects
Does not appear to inhibit adrenal steroidogenesis[32]b
Has no apparent effect on blood glucose concentrations[32]b
Gastrointestinal effects
Inhibits gastric emptying and gastrointestinal transit times[22]a
Ocular effects
Reduces intraocular pressure[33]b

a In healthy volunteers.[14-22]

b In pts undergoing various procedures or surgery.[23-40]

BP = blood pressure.

Mean HR was reduced by 1.3–7.8 beats per minute (bpm) from baseline values in dexmedetomidine recipients; in contrast, mean HR was elevated by 2.1–12.8 bpm from baseline in placebo recipients, with significant between-group differences observed from 10 minutes to 15 hours following the initiation of the study medication (p-value not reported).[41] There was no evidence of a rebound effect, with both BP and HR gradually returning to baseline levels following the cessation of dexmedetomidine.[41]

Patients receiving dexmedetomidine generally remained haemodynamically stable, according to the results of two studies in patients undergoing awake fibre-optic intubation (AFOI)[42] or a variety of diagnostic or surgical procedures requiring monitored anaesthesia care (MAC)[43] [see section 4.2 for study design and full treatment regimen details]. There was no significant difference in haemodynamic stability (broadly defined as the time that SBP and HR were outside of the stable range) following sedation with dexmedetomidine versus

placebo. (In both studies, intravenous midazolam was administered to those patients in whom sedation could not be maintained.[42,43])

Dexmedetomidine had minimal effects on respiratory function (see table I and section 5).

3. Pharmacokinetic Properties

Unless otherwise stated, pharmacokinetic studies of dexmedetomidine appear to have been conducted in healthy volunteers and reported in the US prescribing information.[7] However, the pharmacokinetic profile of dexmedetomidine appears to be generally similar in patients and healthy volunteers. For instance, in a study of ten postsurgical patients in an intensive care setting, the mean pharmacokinetics of dexmedetomidine (administered as a loading dose of ≈0.4 μg/kg infused over 10 minutes followed by a maintenance infusion of 0.7 μg/kg/hour) did not differ from those historically observed in healthy volunteers, with the exception of the steady-state volume of distribution (V_{ss}) [172.8 vs 102.4 L].[44] The pharmacokinetics of dexmedetomidine in paediatric patients have not yet been assessed.[7]

The main pharmacokinetic properties of intravenous dexmedetomidine are summarized in table II. According to the US prescribing information, dexmedetomidine exhibits linear pharmacokinetics in the 0.2–0.7 μg/kg/hour dosage range when infused for up to 24 hours.[7]

Following intravenous administration, dexmedetomidine is rapidly distributed, with a distribution half-life ($t_{½}$) of approximately 6 minutes and a V_{ss} of approximately 118 L.[7]

In healthy male and female volunteers, an average of 94% of the administered dexmedetomidine was bound to plasma proteins; this was consistent across different plasma dexmedetomidine concentrations.[7] The plasma protein binding of dexmedetomidine was significantly (no p-value reported) reduced in patients with hepatic impairment compared with healthy volunteers.[7] *In vitro*, digoxin, fentanyl, ketorolac, lidocaine and theophylline exerted a negligible effect on the plasma protein binding of dexmedetomidine; the plasma protein binding of digoxin, ibuprofen, phenytoin, propranolol, theophylline and warfarin was not significantly displaced by dexmedetomidine *in vitro*.[7]

Dexmedetomidine undergoes almost complete biotransformation; very little is excreted unchanged in the faeces and urine.[7] The biotransformation of dexmedetomidine involves cytochrome P450 (CYP)-mediated metabolism and direct glucuronidation. The major metabolic pathways include direct N-glucuronidation to inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6) to 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine and 3-carboxy-dexmedetomidine; and N-methylation to 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine and dexmedetomidine-N-methyl O-glucuronide.[7]

Following intravenous administration, dexmedetomidine had an estimated clearance of

Table II. Pharmacokinetic parameters of intravenous dexmedetomidine (DEX) administered as a loading dose followed by a maintenance infusion for up to 24 hours.[7] Study population not reported

Treatment regimen		Total treatment duration (h)	Parameter (mean)			
loading dose (μg/kg)[a]	maintenance rate (μg/kg/h)[b]		Css[c] (ng/mL)	V_{ss} (L)	$t_{½}$ (h)	CL (L/h)
DEX 0.5	DEX 0.17	12	0.27	88.7	1.78[d]	46.3
DEX 0.5	DEX 0.17	24	0.27	102.4	2.22[d]	43.1
DEX 1.0	DEX 0.33	24	0.67	93.6	2.23[d]	35.3
DEX 2.2	DEX 0.70	24	1.37	99.6	2.50[d]	36.5

a Infused over 10 min (DEX 0.5 and 1.0) or 35 min (DEX 2.2).

b To achieve a target plasma concentration of 0.3 ng/mL (DEX 0.17), 0.6 ng/mL (DEX 0.33) or 1.25 ng/mL (DEX 0.70).

c Calculated based on post-dose sampling from 2.5 to 9 hours for the 12-hour infusion and from 2.5 to 18 hours for the 24-hour infusions.

d Harmonic mean value.

Css = steady-state plasma concentration; **CL** = clearance; **$t_{½}$** = terminal elimination half-life; **V_{ss}** = steady-state volume of distribution.

approximately 39 L/h (with an associated mean bodyweight of 72 kg) and a terminal elimination $t_{½}$ of ≈2 hours (study population not reported).[7] Nine days following the intravenous administration of radiolabeled dexmedetomidine, an average of 95% and 4% of the radioactivity was recovered in the urine and faeces, with ≈85% of the radioactivity recovered in the urine excreted within 24 hours of the infusion.[7] No unchanged dexmedetomidine was detected in the urine.[7]

Age, sex or severe renal impairment does not appear to affect the pharmacokinetics of dexmedetomidine.[7] The pharmacokinetics (including V_{ss} and elimination clearance) of dexmedetomidine in patients with severe renal impairment (creatinine clearance <30 mL/min [<1.8 L/h]; n = 6) did not significantly differ from those in healthy volunteers (n = 6), with the exception of the mean elimination $t_{½}$, which was significantly ($p < 0.05$) shorter in patients with severe renal impairment than in healthy volunteers (113.4 vs 136.5 minutes).[45]

Hepatic impairment reduces the clearance of dexmedetomidine; in patients with mild, moderate or severe hepatic impairment, mean clearance values were 74%, 64% and 53% of those observed in healthy volunteers.[7] Therefore, although dexmedetomidine is dosed for effect, dosage adjustment should be considered in these patients (see section 6).[7]

No evidence of clinically relevant CYP-mediated drug interactions was observed in human liver microsomes.[7]

4. Therapeutic Efficacy

4.1 In Mechanically Ventilated Patients in an Intensive Care Setting

The therapeutic efficacy of intravenous dexmedetomidine as a short-term sedative for post-surgical patients in an intensive care setting has been evaluated in two randomized, double-blind, placebo-controlled, multinational studies (n > 350).[41,46,47] Data from one study[46,47] are available from medical reviews released by the US FDA. Supplementary data from these studies have been procured from the US manufacturer's prescribing information.[7]

Eligible patients (aged 17–88[41] or ≥18[47] years) were enrolled if they were scheduled for a surgical procedure that was expected to require a minimum of 6 hours of post-surgical assisted ventilation. Among other criteria, patients were excluded or discontinued if they required the utilization of neuromuscular blocks or epidural or spinal analgesia,[41,47] or had received midazolam for anaesthesia maintenance.[47] Four types of surgical procedures were performed: cardiac, head and neck, laparotomy and other.[41,47]

Where reported,[41] patients remained on the ventilator for a minimum of 6 hours following entry into the intensive care unit (ICU). Commencement of the study medication occurred as soon as possible following ICU entry, but within a maximum of 1 hour; it was continued through weaning and extubation, and for a minimum of 6 hours post-extubation, with a total treatment duration of <24 hours.[41,46,47] The requirement (and utilization) of sedatives beyond this timepoint was not reported. Where described,[47] the mean total infusion duration of dexmedetomidine and placebo was 16.6 and 15.7 hours.

Patients were randomized to receive dexmedetomidine (n = 203[41] and 178[7]) or placebo (n = 198[41] and 175[7]), with the infusion rate adjusted to achieve and/or maintain a Ramsay Sedation Scale (RSS) score of ≥3. The RSS has scores ranging from 1 (patient anxious, agitated or restless) to 6 (asleep, no response).[41] In patients in whom sedation could not be maintained despite receiving the maximum infusion rate (0.7 μ/kg/hour), intravenous propofol[41] or intravenous midazolam[46] was administered. Details of the various treatment regimens are shown in table III. Following extubation, the infusion rate was adjusted to achieve a RSS of ≥2.[41,47]

There were no restrictions on intraoperative drug utilization;[41] patients requiring sedation from the operating theatre to the ICU (prior to the commencement of the study medication) were permitted to receive intravenous propofol 0.2 mg/kg[41] or intravenous midazolam (dose not reported).[47]

The primary or co-primary efficacy endpoints were the total dose of rescue sedation (intravenous propofol[41] and intravenous midazolam[46,47])

Table III. Efficacy of intravenous dexmedetomidine (DEX) as a short-term sedative for post-surgical patients (pts). Results of two randomized, double-blind, placebo (PL)-controlled, multinational studies that are fully published[41] or available from the US FDA website,[46,47] with supplemental data from the US manufacturer's prescribing information.[7] See text for study design details. Efficacy endpoints relate to the utilization of rescue sedation,[a] with results reported in the intent-to-treat population

Study	Treatment[b]	No. of pts	Assisted ventilation period			Study medication administration period	
			mean total dose of rescue sedation required (mg)	pts not requiring rescue sedation (%)	mean rate of rescue sedation (mg/h)	mean total dose of rescue sedation required (mg)	mean rate of rescue sedation (mg/h)
Martin et al.[41]	DEX	203	71.6***[c]	60.1**	8.6**	80.0**	5.3**
	PL	198	513.2[c]	23.7	65.6	559.8	39.1
US FDA[46,47]	DEX	178	4.8*[c]	60.7**[c]			0.29***
	PL	175	18.6[c]	24.6[c]			1.19

a In those pts in whom the rate of infusion of the study medication was 0.7 μg/kg/h but in whom sedation could not be maintained, a bolus of intravenous PRO 0.2 mg/kg[41] or intravenous MID 0.02 mg/kg[46] could be administered. If sedation remained inadequate following three bolus injections of PRO[41] or MID[46] within a 2 h period,[46] a continuous infusion at a rate of PRO 0.5–4.0 mg/kg/h[41] or MID 0.01–0.02 mg/kg/h[46] could be initiated.

b Pts initially received a loading dose of DEX 1.0 μg/kg or PL infused over 10 min followed by a maintenance infusion of DEX or PL commencing at a rate of 0.4 μg/kg/h and titrated to a rate of 0.2–0.7 μg/kg/h to achieve and/or maintain a RSS score of ≥3.[7,41]

c Primary or co-primary efficacy endpoint.

MID = midazolam; **PRO** = propofol; **RSS** = Ramsay Sedation Scale; * $p < 0.005$, ** $p < 0.001$, *** $p < 0.0001$ vs PL.

required to achieve and/or maintain a RSS score of ≥3 during the assisted ventilation period,[41,46,47] and the percentage of patients who achieved a RSS of ≥3 during the assisted ventilation period without the utilization of additional rescue medication.[7,46,47]

Incremental doses of intravenous morphine 2 mg, repeated as necessary, were administered to those patients experiencing pain throughout the study,[41,46,47] with paracetamol (acetaminophen) administered, when clinically necessary, following extubation.[46] The requirement for analgesia was determined individually by either direct communication with the patient or by the indirect assessment of pain symptoms (e.g. excessive movement, hypertension, sweating or tachycardia).[41,46]

Data are reported for the intent-to-treat (ITT) population.[41,47]

Intravenous dexmedetomidine was effective as a short-term sedative for post-surgical patients, with a significantly lower mean total dose of rescue sedation (intravenous propofol[41] or intravenous midazolam[46,47]) required to achieve and/or maintain a RSS score of ≥3 during the assisted ventilation period (primary or co-primary efficacy endpoint) following dexmedetomidine than placebo therapy (table III). Moreover, a significantly ($p < 0.001$) higher percentage of dexmedetomidine than placebo recipients acquired and/or maintained a RSS score of ≥3 without rescue sedation with intravenous propofol[41] or intravenous midazolam (co-primary efficacy endpoint)[7,46,47] [table III].

The mean rate of rescue sedation with intravenous propofol required to achieve and/or maintain a RSS score of ≥3 during the assisted ventilation period was significantly lower following dexmedetomidine than placebo therapy (table III).[41] Moreover, where stated, the mean total dose[41] and mean rate[41,47] of rescue sedation with intravenous propofol[41] or intravenous midazolam[47] required during the study medication administration period was significantly lower following dexmedetomidine than placebo therapy (table III).

In the larger study, patients receiving dexmedetomidine or placebo were sedated during the assisted ventilation period to a mean RSS score of 3.4 and 3.1; 3% and 7% of patients in the respective treatment groups had a RSS score of 1 at least once.[41] Although a statistically significant difference (p-value not reported) in the mean RSS score was observed between patients receiving dexmedetomidine and those receiving placebo during the study medication administration period of

the smaller study (3.6 vs 3.3), this difference was deemed not clinically important.[47]

Sedation with dexmedetomidine was also effective in terms of the total dose of morphine administered and the Patient Management Index (PMI) score.[41,46,47] Dexmedetomidine recipients required significantly ($p < 0.05$) less additional pain medication (morphine) [assessed as mean total dose] than placebo recipients during the assisted ventilation period and the period from extubation to the end of the administration of the study medication.[41,46,47] There was no statistically significant between-group difference in the total dose of morphine (assessed as mean rate) required during the study medication administration period for those patients who did not receive intravenous midazolam.[47] However, a statistically significant ($p < 0.05$) between-group difference in the total dose of morphine (assessed as mean rate) required during the study medication administration period was observed among those patients who received up to 4 mg of intravenous midazolam during the assisted ventilation period.[47]

Mean PMI scores were significantly ($p < 0.05$) lower in patients receiving dexmedetomidine than in those receiving placebo, with lower scores corresponding to greater apparent calm, ease of communication (i.e. easier to arouse to answer questions or respond to neurological tests) and overall manageability of care, and greater tolerance of the endotracheal tube, the ventilator and the ICU.[41,46,47]

According to Kaplan-Meier estimates, no significant differences between dexmedetomidine and placebo were predicted in either the median duration of weaning from the ventilator or the median time to extubation.[41,46,47]

At the end of their stay in the ICU, 36% and 31% of patients receiving dexmedetomidine and placebo in the larger study were completely comfortable during the sedation period, with 23% and 34% of patients remembering pain, 33% and 37% remembering discomfort from the endotracheal tube, 36% and 46% remembering people, and 23% and 34% remembering noise.[41] The ICU experience was not remembered by 31% of dexmedetomidine recipients and 25% of placebo recipients.[41] The overall experience was rated as 'better than expected' by 61% of dexmedetomidine and 52% of placebo recipients in the smaller study, from assessable patient numbers of 170 and 164.[47]

4.2 During Procedural Sedation

The therapeutic efficacy of intravenous dexmedetomidine as the primary sedative for patients undergoing AFOI[42] or in non-intubated patients undergoing a variety of diagnostic or surgical procedures requiring MAC[43] has been assessed in two randomized, double-blind, placebo-controlled, multicentre studies ($n > 100$). These data are supplemented with information from the US prescribing information.[7]

Eligible adult (aged ≥18 years) patients were enrolled if they were scheduled for an elective AFOI due to an anticipated difficult airway prior to a surgical or diagnostic procedure[7,42] or elective surgeries and procedures (expected to last at least 30 minutes) performed in an operating room or a procedure room and requiring a local anaesthetic block with MAC and an anaesthesiologist in attendance.[43] Patients in both studies had an American Society of Anesthesiologists (ASA) physical status of I–IV.[42,43] In the AFOI study, patients were stratified according to the Mallampati classification (Class I–III vs Class IV) and the ASA classification (Class I–III vs Class IV) to ensure balanced treatment allocation based on airway difficulty and the patient's physical status.[42]

Among other criteria, patients who received general anaesthesia within 7 days of study entry,[43] α_2-adrenergic receptor agonists and antagonists within 14 days of the scheduled surgery/procedure,[42,43] or an oral[42] or intravenous[42,43] opioid within 1 hour or an oral[43] or intramuscular[42,43] opioid within 4 hours of the commencement of the study drug were excluded.

Patients undergoing AFOI were randomized to receive dexmedetomidine ($n = 55$) or placebo ($n = 50$) to achieve a RSS score of ≥2.[42] Administration of the study medication commenced 15 minutes prior to airway topicalization (for AFOI) and continued throughout intubation, with glycopyrrolate 0.1 mg administered prior to dexmedetomidine or placebo infusion.[42] Following the achievement of airway anaesthesia with lidocaine and confirmation of a suppressed gag reflex, AFOI was

performed.[42] The study medication was discontinued upon completion of the AFOI, with general anaesthesia then induced and the scheduled procedure/surgery completed.[42] The mean duration of dexmedetomidine and placebo infusion was 37.7 and 41.5 minutes.[42]

Non-intubated patients undergoing a variety of diagnostic or surgical procedures requiring MAC were randomized to receive dexmedetomidine (0.5 μg/kg loading dose, n = 134; 1.0 μg/kg loading dose, n = 129) or placebo (n = 63), with the infusion rate adjusted to achieve an Observer's Assessment of Alertness/Sedation Scale (OAA/S; scale of 1 [deep sleep] to 5 [alert])[48] score of ≤4.[43] All patients received a local anaesthetic block prior to the surgery/procedure (at least 15 minutes following commencement of the infusion and when an OAA/S score of ≤4 was observed).[43] Intravenous fentanyl 25 μg boluses, repeated as necessary, were administered to those patients expressing a pain score (scale 0–10; 0 = no pain and 10 = worst pain) of ≥3 during the infusion and ≥4 in the post-anaesthesia care unit (PACU) or to those in whom the investigator determined the presence of pain when verbal communication was not possible.[43] The study medication was discontinued when the patient left the operating room; patients remained in the post-operative unit for at least 1 hour following discontinuation.[43] The mean duration of study medication infusion was 97.0, 102.3 and 105.6 minutes in the dexmedetomidine 0.5 μg/kg, 1.0 μg/kg and placebo groups, respectively.[43]

In both studies, intravenous midazolam was administered to those patients in whom sedation could not be maintained.[42,43] Details of the various treatment regimens are shown in table IV.

The primary efficacy endpoint was the percentage of patients requiring rescue sedation with intravenous midazolam to achieve and/or maintain a RSS score of ≥2 throughout the study medication infusion period in the AFOI study[42] and the percentage of patients not requiring rescue sedation with intravenous midazolam to achieve and/or maintain an OAA/S score of ≤4 in the MAC study.[43]

Data are reported for the modified ITT population (all randomized patients who received the study medication and had at least one post-baseline efficacy measurement).[42,43] Statistical analysis adjusted for surgery/procedure type (arteriovenous fistula, vascular stent or hernia surgery, breast biopsies, excision of lesions and plastic surgery, ophthalmic or orthopaedic procedures).[43]

Intravenous dexmedetomidine was effective as a primary sedative in adult patients undergoing AFOI[42] or a variety of diagnostic or surgical procedures requiring MAC.[43] In the AFOI study,[42] significantly fewer dexmedetomidine than placebo recipients required rescue sedation with intravenous midazolam to achieve and/or maintain a RSS score of ≥2 during AFOI (table IV). In the MAC study,[43] rescue sedation with intravenous midazolam was not required to achieve and/or maintain an OAA/S score of ≤4 during MAC by significantly more dexmedetomidine than placebo recipients (table IV). Of the two placebo recipients that did not require rescue sedation with intravenous midazolam in the MAC study, both underwent cataract surgery.[43]

According to a prespecified subanalysis of the AFOI study, significantly fewer dexmedetomidine than placebo recipients with Mallampati Class IV airways required rescue sedation with intravenous midazolam during AFOI (33.3% [4/12] vs 91.7% [11/12]; $p < 0.001$).[42] Moreover, in a prespecified subanalysis of the MAC study, significant (p-values not reported) between-group differences for both dexmedetomidine treatment groups versus placebo in the percentage of patients not requiring rescue sedation with intravenous midazolam during MAC were observed across all surgical subtypes, with the exception of the breast biopsies, excision of lesions and plastic surgery subgroup in which there was no significant difference between the dexmedetomidine 0.5 μg/kg loading dose treatment group and placebo.[43]

In terms of the secondary efficacy endpoints detailed in table IV (including the mean total dose of midazolam,[42,43] the percentage of patients requiring further sedation [in addition to dexmedetomidine or placebo and midazolam][42,43] and/or the time from the start of the study medication to the administration of midazolam[43]), primary sedation with intravenous dexmedetomidine was effective in adult patients, with generally significant

Table IV. Efficacy of intravenous dexmedetomidine (DEX) as the primary sedative for patients (pts) undergoing awake fibre-optic intubation[42] or a variety of diagnostic or surgical procedures requiring monitored anaesthesia care.[43] Results of two randomized, double-blind, placebo (PL)-controlled, multicentre studies; analyses are for the modified intent-to-treat population. All agents were administered intravenously, with the loading dose administered over 10 min

Study	Treatment (loading dose [μg/kg])	No. of pts	Primary endpoint (% of pts)		Mean total MID dose (mg)	Median time to administration of MID (min)	Pts requiring further sedation (%)
			requiring MID[a]	not requiring MID[a]			
Bergese et al.[42]	DEX[b]	55	47.3**		1.07**		0
	PL[b]	50	86.0		2.85		8.0
Candiotti et al.[43]	DEX (0.5)[c]	134		40.3**	1.4**	40.0**	3.0*
	DEX (1.0)[c]	129		54.3**	0.9**	114.0**	1.6*
	PL[c]	63		3.2	4.1	20.0	11.1

a A bolus of MID 0.5 mg could be administered as rescue medication.[42,43] MID administration was repeated until the RSS score was ≥2[42] or the OAA/S score was ≤4.[43] Those pts inadequately sedated following MID totalling 0.2 mg/kg received other rescue medication at the anaesthesiologist's discretion and discontinued from the study.[42] If clinically indicated, the pt could be converted to an alternative sedative or anaesthetic therapy and the study medication discontinued at any time.[43]

b Pts received a loading dose of DEX 1.0 μg/kg or PL followed by DEX or PL 0.7 μg/kg/h to achieve a RSS score of ≥2.

c Pts received a loading dose of DEX 0.5 or 1.0 μg/kg or PL followed by DEX or PL commencing at 0.6 μg/kg/h and titrated from 0.2 to 1.0 μg/kg/h.[43]

MID = midazolam; **OAA/S** = Observer's Assessment of Alertness/Sedation Scale; **RSS** = Ramsay Sedation Scale; * $p < 0.05$, ** $p < 0.001$ vs PL.

between-group differences observed in favour of dexmedetomidine over placebo.[42,43] In the MAC study, significantly ($p < 0.001$) fewer dexmedetomidine 0.5 and 1.0 μg/kg loading dose recipients than placebo recipients required rescue fentanyl (for pain) [59.0% and 42.6% vs 88.9%]; in addition, the mean total dose of fentanyl required was significantly ($p < 0.001$) lower in the dexmedetomidine 0.5 and 1.0 μg/kg loading dose treatment groups than in the placebo group (8.48 and 83.6 vs 144.4 μg).[43]

Furthermore, prespecified subanalyses demonstrated significant differences favouring dexmedetomidine over placebo in the mean total dose of rescue sedation with intravenous midazolam required during AFOI in patients with Mallampati IV airways ($p < 0.005$)[42] or during MAC across the surgical subtypes (p-value not reported)[43] or in the mean dose of rescue fentanyl required during MAC across the surgical subtypes ($p < 0.005$).[43]

In the AFOI study, dexmedetomidine recipients had lower mean RSS scores, assessed 15 minutes following initiation of the study medication and prior to topicalization, than placebo recipients (2.1 vs 1.7; $p = 0.001$).[42]

No significant difference in the median time to recovery and readiness for discharge from the PACU was observed between the dexmedetomidine 0.5 and 1.0 μg/kg loading dose treatment groups and the placebo group in the MAC study (29.0 and 25.0 vs 14.0 minutes).[43] There was also no significant difference between the dexmedetomidine and placebo treatment groups in the incidence of postoperative nausea and vomiting.[43] Significantly ($p < 0.05$) more placebo than dexmedetomidine 1.0 μg/kg loading dose recipients required additional pain medication in the PACU.[43]

Across the two studies, there were no significant differences observed between the dexmedetomidine and placebo treatment groups in the anaesthesiologists' assessment of ease of intubation,[42] haemodynamic stability,[42,43] patient cooperation[42,43] and respiratory stability;[43] however, in the MAC study, the ease of maintenance of sedation visual analogue scale scores were significantly ($p < 0.001$) lower for both dexmedetomidine treatment groups versus placebo (2.8 and 2.2 vs 4.4 cm).[43]

Following surgery in the MAC study, patients in the dexmedetomidine 1.0 μg/kg loading dose treatment group had significantly lower mean anxiety scores (assessed utilizing the Anxiety Assessment Scale with scores ranging from 0 [no anxiety] to 10 [extreme anxiety]) than those in the placebo group (1.0 vs 1.9; $p = 0.007$).[43]

Twenty-four hours following discontinuation, significantly ($p \leq 0.001$) more patients in both the

dexmedetomidine 0.5 and 1.0 μg/kg loading dose treatment groups than the placebo group in the MAC study were satisfied with their sedation according to the Iowa Satisfaction with Anesthesia Scale (a 6-point scale with scores ranging from −3 to +3) [2.0 and 2.0 vs 1.4].[43] The majority of patients in the AFOI study did not recall feeling pain during intubation and were satisfied with their sedation (no quantitative data or statistical analysis reported).[42] In the same study, 60.8% of dexmedetomidine recipients and 57.4% of placebo recipients remembered placement of the fibre-optic scope.[42]

5. Tolerability

Intravenous dexmedetomidine was generally well tolerated when utilized in mechanically ventilated patients in an intensive care setting[41,46,47] and for procedural sedation in non-intubated patients.[42,43] As the tolerability profile of dexmedetomidine is well established, discussion in this section focuses on tolerability data derived from clinical studies discussed in section 4,[41-43] with supplementary data from pooled analyses procured from the US manufacturer's prescribing information.[7] Data from a study of postoperative delirium in mechanically ventilated patients in an intensive care setting are also reviewed.[49]

The most frequently reported treatment-emergent adverse events that occurred with a ≥2% frequency across the clinical studies were bradycardia, dry mouth and hypotension.[7]

According to the US manufacturer's prescribing information, clinically significant episodes of bradycardia and sinus arrest have been observed following the administration of dexmedetomidine to healthy volunteers with high vagal tone and following the administration of dexmedetomidine via different routes, including rapid intravenous or bolus administration (see section 6).[7]

5.1 In Mechanically Ventilated Patients in an Intensive Care Setting

When utilized as a primary sedative in post-surgical patients in an intensive care setting, intravenous dexmedetomidine was generally well tolerated.[7,41] The treatment-emergent adverse events occurring most frequently (>5%) in dexmedetomidine recipients (and with a numerically higher incidence than in placebo recipients) were hypotension, nausea and bradycardia, according to a pooled analysis (figure 1).[7]

The overall tolerability profile of dexmedetomidine in the pooled analysis[7] was consistent with that observed in the fully published clinical study.[41] In this study, the incidence of at least one treatment-emergent adverse event following sedation with dexmedetomidine did not significantly differ from that observed following placebo (60% [121 of 203 patients] vs 57% [112 of 198]), with the majority of adverse events being of mild or moderate severity.[41] However, sedation with dexmedetomidine was associated with a significantly ($p < 0.005$) higher incidence of hypotension (30% vs 10%) and bradycardia (9% vs 2%) and a significantly ($p < 0.05$) lower incidence of hypertension (12% vs 23%), atelectasis (0.5% vs 5%) and rigours (0.5% vs 4%) than sedation with placebo.[41]

Over half of those dexmedetomidine recipients who developed hypotension did so during or shortly after (within minutes) the loading dose infusion.[41] These episodes generally resolved either without treatment or with changes in positioning and/or fluids or medication.[41] Severe hypotension was reported in 5% and 2% of dexmedetomidine and placebo recipients; the majority of these cases required drug treatment (e.g. inotropic support) to resolve.[41]

Of the 18 dexmedetomidine recipients who experienced bradycardia, seven experienced it during the first hour, with five experiencing it during the loading dose infusion.[41] Six of these 18 dexmedetomidine recipients experienced severe bradycardia and 12 experienced bradycardia considered possibly or probably related to dexmedetomidine.[41] The bradycardia experienced by placebo recipients was not considered severe; three of the four placebo recipients experienced bradycardia considered possibly or probably related to placebo.[41] For the most part, the bradycardia resolved either spontaneously or with medication (e.g. atropine) in both treatment groups.[41]

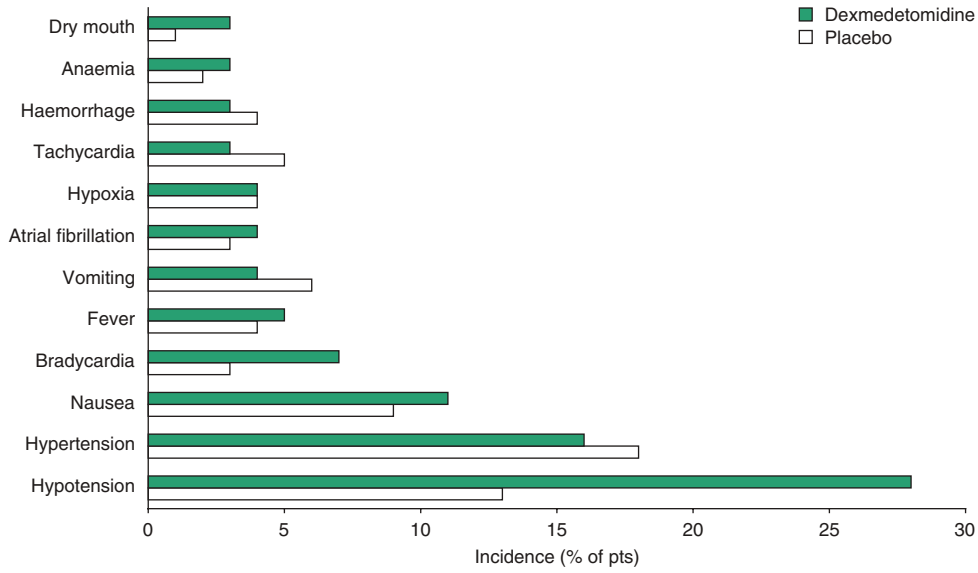

Fig. 1. Tolerability profile of intravenous dexmedetomidine as a short-term sedative for post-surgical patients (pts) in an intensive care setting. Incidence of treatment-emergent adverse events affecting >2% of pts in a pooled analysis[7] of randomized, placebo-controlled studies. Pts received dexmedetomidine (n = 387) or placebo (n = 379) for <24 hours (no further dosage and design details reported).

Approximately two-thirds of those dexmedetomidine recipients who developed hypertension did so during the loading dose infusion; these episodes were generally mild to moderate, lasted <1 hour and resolved without treatment or intervention.[41]

Dexmedetomidine appears to have no effect on respiratory rate and oxygen saturation.[41] Treatment-emergent respiratory system adverse events were reported in 11% of dexmedetomidine recipients and 14% of placebo recipients, with no statistically significant between-group differences in mean respiratory rate (following extubation) and oxygen saturation variability (during the study medication infusion period) observed.[41] Oxygen saturation levels in both treatment groups remained within normal ranges following extubation.[41]

Treatment discontinuations occurred in 6.4% (13 of 203 patients) of dexmedetomidine and 3.5% (7 of 198) of placebo recipients; in four and two of these patients, respectively, the treatment discontinuation was deemed to be possibly related to the study medication.[41] Severe treatment-emergent adverse events were reported in 12% of patients in each treatment group.[41] Death occurred in four patients (three dexmedetomidine recipients and one placebo recipient); all of the events leading to death were deemed unrelated to the study medication.[41]

Postoperative sedation with dexmedetomidine was associated with significantly lower rates of postoperative delirium than midazolam or propofol, according to a randomized, nonblind study in mechanically ventilated patients in an intensive care setting who had undergone cardiac valve procedures with cardiopulmonary bypass.[49] Delirium (primary endpoint) occurred in 3% (1 of 30 patients) of patients receiving dexmedetomidine (administered as a loading dose of 0.4 μg/kg infused over 10 minutes followed by a maintenance infusion at a rate of 0.2–0.7 μg/kg/hour) versus 50% (15 of 30) and 50% (15 of 30) of patients receiving midazolam (administered as an infusion at a rate of 0.5–2 mg/hour) and propofol (administered as an infusion at a rate of 25–50 μg/kg/minute) [both $p < 0.001$; per-protocol population].[49] Delirium was diagnosed as the presence of symptoms consistent with the *Diagnostic and Statistical Manual of Mental Disorders IV*, text revision criteria for the previous 24 hours.[49] Those patients developing

delirium experienced significantly ($p < 0.001$) longer stays in the ICU (4.1 vs 1.9 days) and the hospital (10.0 vs 7.1 days) than those patients not experiencing delirium.[49]

5.2 During Procedural Sedation

As expected, hypotension was also the most frequently occurring treatment-emergent adverse event associated with the utilization of intravenous dexmedetomidine as a primary sedative for procedural sedation, according to a pooled analysis[7] of two studies[42,43] discussed in section 4.2. Figure 2 presents the incidence of treatment-emergent adverse events that occurred with a >2% frequency in this pooled analysis.[7] The majority of these events were mild or moderate in severity.[42,43]

The incidence of treatment-emergent adverse events did not significantly differ between dexmedetomidine and placebo recipients in the AFOI study (63.6% [35/55] vs 58.0% [29/50]).[42] In the MAC study,[43] no between-group differences in the incidence of treatment-emergent adverse events either intra-operatively or in the PACU were observed.[43]

Sedation with dexmedetomidine resulted in a predictable reduction in BP and HR values (see section 2), with protocol-defined hypotension (see figure 2 for definitions) [all cases mild or moderate in severity[43]] the most frequently reported adverse event in dexmedetomidine recipients.[42,43] The incidence of protocol-defined hypotension was significantly higher (27.3% vs 6.0%; $p = 0.0042$) and that of protocol-defined tachycardia significantly lower (7.3% vs 24.0%; $p = 0.0277$) in dexmedetomidine than placebo recipients in the AFOI study (see figure 2 for definitions).[42] No significant differences between dexmedetomidine and placebo recipients in the

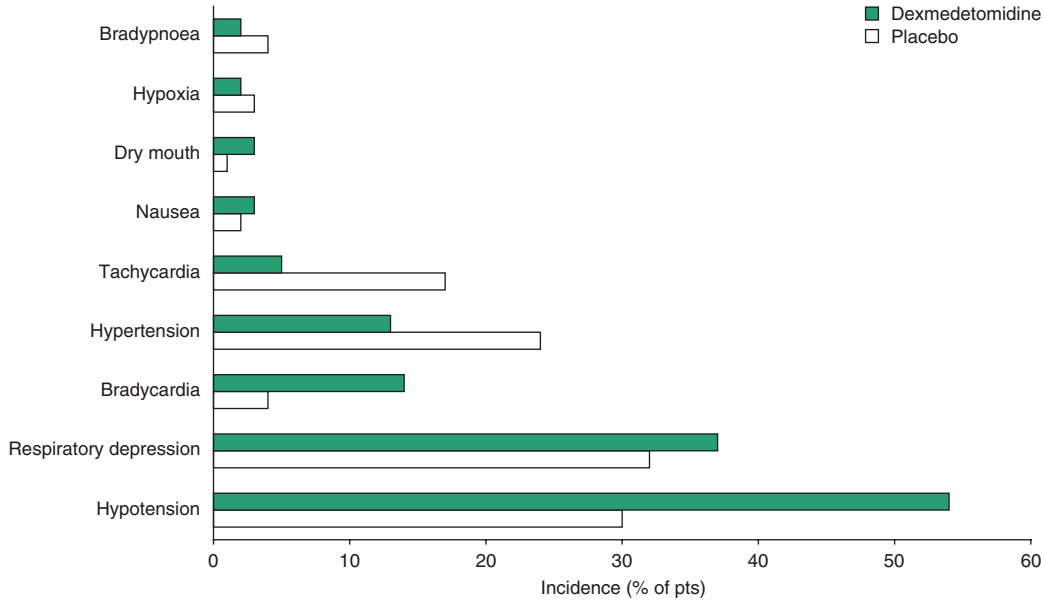

Fig. 2. Tolerability profile of intravenous dexmedetomidine as the primary sedative for patients (pts) undergoing awake fibre-optic intubation or a variety of diagnostic or surgical procedures requiring monitored anaesthesia care. Incidence of treatment-emergent adverse events affecting >2% of pts in a pooled analysis[7] of data from two clinical studies.[42,43] Pts received dexmedetomidine (n = 318) or placebo (n = 113); see section 4.2 for study design and full treatment regimen details. Bradycardia was defined as a heart rate (HR) of <40 beats per minute (bpm) or ≤30% lower than baseline; hypertension was defined as a systolic blood pressure (SBP) of >180 mmHg or ≥30% higher than baseline, or a diastolic blood pressure (DBP) of >100 mmHg; hypotension was defined as a SBP of <80 mmHg or ≤30% lower than baseline, or a DBP of <50 mmHg; hypoxia was defined as an oxygen saturation of <90% or a 10% decrease from baseline; respiratory depression was defined as a respiratory rate of <8 breaths per minute or a >25% decrease from baseline; and tachycardia was defined as a HR of >120 bpm or ≥30% higher than baseline.

incidence of protocol-defined bradycardia (7.3% vs 0%) or hypertension (23.6% vs 28.0%) were observed (see figure 2 for definitions).[42]

During the infusion period of the MAC study, the incidence of respiratory depression was significantly ($p = 0.018$) lower with dexmedetomidine loading doses of 0.5 or 1.0 μg/kg than with placebo (3.7% and 2.3% vs 12.7%).[43]

The coadministration of dexmedetomidine and fentanyl or midazolam in the MAC study was not associated with increased bradycardia, hypotension or respiratory depression; no patient required a reversal agent for midazolam or an opioid.[43] Moreover, no significant elevation in the incidence of bradycardia or hypotension was observed following the administration of dexmedetomidine to patients receiving long-term antihypertensive therapy, including β-adrenergic receptor antagonists.[43] Of the 18 dexmedetomidine recipients receiving concomitant long-term β-adrenergic receptor antagonist therapy in the AFOI study, one experienced protocol-specified bradycardia.[42]

For the most part, the incidence of intervention (titration of the study medication, a bolus of intravenous fluid or pharmacological therapy) for bradycardia, hypertension, hypotension or tachycardia during the study medication administration period in the MAC study did not significantly differ between patients receiving a loading dose of dexmedetomidine 0.5 or 1.0 μg/kg and those receiving placebo; intervention was required in 0–11.9%, 0–8.5% and 0–4.8% of patients in the respective treatment groups.[43] However, a significantly ($p < 0.05$) higher proportion of dexmedetomidine 0.5 μg/kg loading dose recipients than placebo recipients required intervention for hypotension (11.9% [16/134] vs 3.2% [2/63]); in the dexmedetomidine 1.0 μg/kg loading dose treatment group, the incidence of hypotension requiring intervention was not significantly different than that in the placebo group.[43] No intervention for respiratory depression was required in this study.[43]

During infusion of the study medication in the AFOI study, there was no significant difference between dexmedetomidine and placebo recipients in the proportion of patients requiring intravenous fluids or medication (i.e. ephedrine, esmolol, nicardipine or phenylephrine) for BP or HR (12.7% vs 8.0%).[42]

Treatment discontinuations occurred in five dexmedetomidine 0.5 μg/kg loading dose recipients, six dexmedetomidine 1.0 μg/kg loading dose recipients and six placebo recipients in the MAC study.[43] One patient in each treatment group in the AFOI study discontinued the study medication owing to hypertension.[42]

Serious treatment-emergent adverse events were reported by three patients (treatment group not reported) during the follow-up period (24 hours following the end of the procedure) of the MAC study; these were deemed by the investigator to be unrelated to the study medication.[43] In the AFOI study, no serious treatment-emergent adverse events were reported in either treatment group.[42] No deaths were reported in either of the two studies.[42,43]

In the MAC study, the differences between the dexmedetomidine and placebo treatment groups in cardiac monitoring, laboratory profiles and ECG recordings were considered unremarkable.[43]

6. Dosage and Administration

Dexmedetomidine is indicated in the US for the sedation of initially intubated and mechanically ventilated adult patients in an intensive care setting and in non-intubated adult patients prior to and/or during surgical and other procedures.[7] The prescribing information for intravenous dexmedetomidine differs in the other countries in which it has been approved. Local prescribing information should be consulted for detailed information, including contraindications, dosages, drug interactions, precautions and use in special patient populations.

Recommended loading and maintenance dosages of dexmedetomidine in the US are summarized in table V; dosage adjustments may be required in elderly patients or those with hepatic impairment.[7] The pharmacokinetics, efficacy and tolerability of dexmedetomidine in children and adolescents aged <18 years have not been established; therefore, dexmedetomidine should not be utilized in this population.[7] Dexmedetomidine is

Table V. Recommended dosage regimens of intravenous dexmedetomidine in adult patients (pts) aged ≥18 y, based on the US prescribing information[7]

Indication	Dexmedetomidine dosage	
	loading	maintenance
Intensive care setting sedation		
Adult pts	<1.0 μg/kg infused over 10 min	0.2–0.7 μg/kg/h titrated to achieved the required level of sedation and infused for no longer than 24 h
Pts converting from alternate sedative therapy	May not be required	Administer as per adult pts
Pts aged >65 y	Consider a dose reduction	Consider a dosage reduction
Pts with impaired hepatic function	Consider a dose reduction	Consider a dosage reduction
Procedural sedation		
Adult pts	1.0 μg/kg (0.5 μg/kg for less invasive procedures [e.g. ophthalmic surgery]) infused over 10 min	Commence at 0.6 μg/kg/h and titrate from 0.2 to 1.0 μg/kg/h to achieve the desired level of sedation
AFOI pts	1.0 μg/kg infused over 10 min	0.7 μg/kg/h is recommended until the endotracheal tube is secured
Pts aged >65 y	0.5 μg/kg infused over 10 min	Consider a dosage reduction
Pts with impaired hepatic function	Consider a dose reduction	Consider a dosage reduction

AFOI = awake fibre-optic intubation.

not indicated for infusions longer than 24 hours in duration; to achieve the desired level of sedation, the rate of the maintenance infusion should be adjusted.[7] Mechanically ventilated patients do not need to be discontinued from sedation with dexmedetomidine prior to extubation.[7]

Patients should be continuously monitored while receiving dexmedetomidine, with the administration of this agent only undertaken by a person skilled in the management of patients in the intensive care or operating room setting.[7]

As physical compatibility has not yet been established, dexmedetomidine should not be infused through the intravenous catheter utilized for blood or plasma.[7] Dexmedetomidine has been shown to be incompatible when administered with amphotericin B and diazepam; a reduction in the dosage of concomitantly administered dexmedetomidine and anaesthetics, hypnotics, opioids or sedatives may be required owing to potential pharmacodynamic interactions.[7]

The utilization of dexmedetomidine has been associated with serious episodes of bradycardia, hypotension, sinus arrest and transient hypertension (section 5).[7] Transient hypertension was primarily observed during the infusion of the loading dose of dexmedetomidine in association with the initial, peripheral vasoconstrictive effects of this agent; the treatment of transient hypertension is often unnecessary.[7]

Caution is advised when administering dexmedetomidine to patients with advanced heart block and/or severe ventricular dysfunction.[7] Caution is also advised during the coadministration of dexmedetomidine and other vasodilators or negative chronotropic agents, although an additive pharmacodynamic effect has not been observed.[7]

7. Place of Dexmedetomidine in Mechanically Ventilated Patients in an Intensive Care Setting and for Procedural Sedation

Providing an optimal level of sedation for an individual patient and a particular procedure is of prime importance,[4,50] with the appropriate level primarily dependent on the acute disease process and any therapeutic and supportive interventions.[51] Agent-specific characteristics, such as pharmacokinetics, potential adverse events (in susceptible patients) and the utilization of sedation-minimizing strategies should also be considered when attempting to optimize sedation.[52]

In an intensive care setting, a frequent target level of sedation is a calm patient who can be easily aroused but in whom the normal sleep-wake cycle is maintained.[51] However, a number of patients may require deeper levels of sedation in order to facilitate mechanical ventilation.[51] Regardless of the sedative agent utilized, the potential for oversedation exists.[52] Excessive sedation carries greater risks and may lead to adverse events, including a prolonged duration of mechanical ventilation and ICU and hospital stays, and an elevated risk of nosocomial infection, particularly when continuous infusions of sedative agents are employed.[52-54] Sedation may also result in cardiac or respiratory depression; such adverse events must be rapidly recognized and appropriately managed to avoid the risk of hypoxic brain damage, cardiac arrest or death.[1] Owing to the redistribution and accumulation of active metabolites, many sedative agents, such as benzodiazepines and opioids, may have a prolonged and unpredictable duration of action in critically ill patients.[8] Thus, caution is advised when administering continuous infusions, as accumulation (of the parent agent or its active metabolites) may produce inadvertent oversedation.[51]

Conversely, inadequate sedation and analgesia are detrimental to the patient and carry the risk of negative outcomes, such as patient discomfort or injury because of a lack of cooperation or adverse physiological or psychological responses to stress.[1,54] The desired level of sedation should therefore be defined at the initiation of therapy and re-evaluated regularly, with active tapering of the infusion rate employed as the clinical condition of the patient changes, in order to prevent the prolonged effects of sedation.[51] The Society of Critical Care Medicine (SCCM)/American Society of Health-System Pharmacists (ASHP) recommend the utilization of sedation guidelines, an algorithm or a protocol.[51]

There is currently no established consensus on the characteristics of an ideal agent for moderate sedation.[4] However, it is accepted that such characteristics would include a rapid onset of action, a predictable pharmacodynamic/pharmacokinetic profile and a quick recovery of cognitive and physical faculties by the patient.[4]

Historically, the sedative agents most frequently administered to provide anxiolysis in an intensive care setting,[52] and those, among others, recommended by the 2002 SCCM/ASHP clinical practice guidelines[51] for sedation, are benzodiazepines, including diazepam, lorazepam and midazolam. However, the characteristics of benzodiazepines, such as distribution, onset and duration of action, potency and the presence or absence of active metabolites, vary.[51] Caution is advised when benzodiazepines are administered via continuous infusion, owing to the accumulation of the parent agent or its active metabolites, resulting in inadvertent oversedation, and the development of tolerance within hours to several days.[51] According to the SCCM/ASHP guidelines, diazepam and midazolam are recommended for the rapid onset of sedation in acutely agitated patients, with midazolam only recommended for short-term utilization because of the unpredictable awakening and time to extubation seen with infusions of more than 48–72 hours' duration.[51] With the slow onset of action of lorazepam, it is of less use for the treatment of acute agitation and is thus recommended for the maintenance of sedation via continuous or intermittent infusion.[51] Owing to the risks of inducing withdrawal symptoms and elevating myocardial oxygen consumption, the routine utilization of a benzodiazepine antagonist, such as flumazenil, is not recommended following prolonged benzodiazepine administration.[51]

Propofol is recommended by the SCCM/ASHP as the preferred sedative when rapid awakening (e.g. for extubation or neurological assessment) is required.[51] As long-term or high-dose propofol administration may result in hypertriglyceridaemia, the SCCM/ASHP recommends triglyceride monitoring following 2 days of propofol infusion.[51]

In terms of procedural sedation, frequently utilized sedative agents such as etomidate, ketamine, midazolam, and the opioids fentanyl (in combination with midazolam) and remifentanil have become the agents of choice because of their ease of utilization, excellent tolerability profiles and predictable action.[2,11]

α_2-Adrenergic receptor agonists (e.g. clonidine, dexmedetomidine) are deemed to produce analgesia

without the motor or sensory blockade associated with local anaesthetics or the dose-limiting adverse events of opioids (e.g. nausea, potential respiratory depression, pruritus and urinary retention).[55] Moreover, α_2-adrenergic receptor agonists may offer an alternative for those patients who develop a tolerance to opioids or those with pain that responds poorly to opioid analgesics, such as sympathetically maintained neuropathic pain.[55] While current clinical evidence supports the utilization of α_2-adrenergic receptor agonists as sedative agents,[54] their role in the sedation of patients in an intensive care setting at the time of publication of the SCCM/ASHP guidelines was yet to be determined.[51]

Dexmedetomidine is a selective α_2-adrenergic receptor agonist with a dose-dependent α_2-selectivity that is approximately 7- to 8-fold greater than that of clonidine[9,10] (section 2). It provides anxiolytic activity via the stimulation of presynaptic α_2-adrenoreceptors at the level of the locus coeruleus.[52] Intravenous dexmedetomidine was effective as a primary sedative in initially intubated and mechanically ventilated patients in an intensive care setting (section 4.1) and in non-intubated patients prior to and/or during surgical and other procedures (section 4.2) according to the results of randomized, double-blind, placebo-controlled, multicentre studies.

Post-surgical patients in an intensive care setting receiving dexmedetomidine required less rescue sedation with intravenous propofol or intravenous midazolam to achieve and/or maintain optimal sedation during the assisted ventilation period versus those receiving placebo (section 4.1). Moreover, significantly more dexmedetomidine than placebo recipients acquired and/or maintained optimal sedation without rescue sedation. Sedation with dexmedetomidine was also effective in terms of the total dose of morphine administered, with dexmedetomidine recipients requiring less morphine than placebo recipients, and the PMI, with dexmedetomidine recipients proving easier to manage than placebo recipients in that they exhibited greater apparent calm and were easier to arouse, and a greater tolerance of the endotracheal tube, the ventilator and the ICU (section 4.1).

Intravenous dexmedetomidine was effective in adult patients undergoing AFOI or a variety of diagnostic or surgical procedures requiring MAC (section 4.2). Compared with the utilization of placebo, the utilization of dexmedetomidine significantly reduces the need for rescue sedation with intravenous midazolam to achieve or maintain optimal sedation (section 4.2). Primary sedation with intravenous dexmedetomidine was also generally significantly more effective than placebo in terms of the secondary efficacy endpoints, including reducing the mean total dose of midazolam and fentanyl administered, reducing the percentage of patients requiring further sedation (in addition to dexmedetomidine or placebo and midazolam) and/or increasing the time from the start of the study medication to the administration of midazolam (table IV). In general, no significant differences were observed between the dexmedetomidine and placebo treatment groups in the anaesthesiologists' assessment of ease of intubation, haemodynamic stability, patient cooperation and/or respiratory stability.

It is worth noting that dexmedetomidine is currently indicated for infusions not exceeding 24 hours in duration;[7] however, obviously, patients in the intensive care setting may require longer-term (>24 hours) sedation. Recently published studies have determined the efficacy of dexmedetomidine in the longer-term sedation of mechanically ventilated patients in the intensive care setting,[56,57] with data from forthcoming[58,59] studies awaited with interest. Studies have also evaluated the efficacy of dexmedetomidine as an adjunct to general anaesthesia during, among others, bariatric surgery[60,61] and cardiovascular surgery;[62-64] however, their discussion is beyond the scope of this review.

Pharmacoeconomic analyses of intravenous dexmedetomidine as the primary sedative for mechanically ventilated patients in an intensive care setting and for procedural sedation in non-intubated patients where the infusion duration was less than 24 hours are currently lacking. However, a cost-minimization analysis in mechanically ventilated patients in an intensive care setting treated for more than 24 hours predicted significantly lower ICU costs with dexmedetomidine than

midazolam, primarily due to reduced ICU stay costs and reduced mechanical ventilation costs.[65] Robust pharmacoeconomic studies are required to establish the cost effectiveness of dexmedetomidine administered for up to 24 hours.

Intravenous dexmedetomidine was generally well tolerated when utilized in mechanically ventilated patients in an intensive care setting and for procedural sedation in non-intubated patients (section 5). Hypotension and bradycardia are two of the most frequently reported adverse events in dexmedetomidine recipients. Indeed, hypotension occurred in significantly more dexmedetomidine than placebo recipients in both indications (sections 5.1 and 5.2), with bradycardia occurring in significantly more dexmedetomidine than placebo recipients among mechanically ventilated patients in an intensive care setting (section 5.1). Hypotension and/or bradycardia usually resolved without intervention. When intervention is required, the US prescribing information recommends decreasing the dexmedetomidine infusion rate or stopping the infusion, increasing the infusion rate of intravenous fluids, elevating lower extremities and utilizing pressor agents.[7] The use of anticholinergic agents should also be considered in patients with bradycardia.[7] The predictable reductions in BP and HR observed in these studies mean that dexmedetomidine may be of particular benefit in certain patient groups (e.g. mechanically ventilated patients in an intensive care setting who are at high risk of postoperative cardiac complications).[41]

Transient hypertension was reported in the clinical studies (sections 5.1 and 5.2). Hypertension usually developed during administration of the dexmedetomidine loading dose (in response to the initial peripheral vasoconstrictive effect of dexmedetomidine[7]), and resolved without intervention.

The loading dose of dexmedetomidine should be infused over 10 minutes (see section 6).[7] It should be noted that the rapid intravenous or bolus administration of dexmedetomidine has been associated with clinically significant episodes of bradycardia and sinus arrest (section 5).[7] This may, therefore, limit the utilization of dexmedetomidine in patients in the intensive care setting requiring very rapid sedation (e.g. agitated patients who are attempting to self-extubate).

Dexmedetomidine was not associated with respiratory depression (section 5). This lack of respiratory depression may make dexmedetomidine a useful option in certain patient groups, such as the morbidly obese.[10] In addition, the lack of respiratory depression seen in mechanically ventilated patients in an intensive care setting who received dexmedetomidine may translate to improved weaning and extubation times.[41] Although no significant difference was seen between dexmedetomidine and placebo recipients in weaning or extubation times (section 4.1), these studies were not designed to examine these endpoints.[41] Additional studies specifically designed to assess these endpoints would be of interest.

In an intensive care setting, up to 80% of patients may experience delirium, which is characterized by an acutely changing or fluctuating mental status, disorganized thinking, inattention and an altered level of consciousness that may or may not be accompanied by agitation.[51] Moreover, inappropriate drug regimens for sedation or analgesia may exacerbate delirium symptoms,[51] with reports of an increased risk of delirium associated with benzodiazepines and propofol.[8] Dexmedetomidine was associated with significantly lower rates of postoperative delirium than midazolam or propofol in patients undergoing cardiac valve procedures with cardiopulmonary bypass, according to a randomized, nonblind study (section 5.1).[49] According to a recently published prospective cohort analysis[66] of 354 patients in an intensive care setting from a randomized, double-blind, multicentre study,[56] the duration of delirium is the strongest independent predictor of death, time on mechanical ventilation and length of stay in the ICU.

In conclusion, intravenous dexmedetomidine provides effective sedation in mechanically ventilated patients in an intensive care setting and effective procedural sedation. It reduces the need for rescue sedation with intravenous propofol or intravenous midazolam and reduces opioid requirements. Sedation with dexmedetomidine is also effective in terms of patient management, with recipients calm and easy to arouse and

manage. Intravenous dexmedetomidine is generally well tolerated when utilized in mechanically ventilated patients in an intensive care setting and for procedural sedation in non-intubated patients. Dexmedetomidine is associated with a lower rate of postoperative delirium than midazolam or propofol; it is not associated with respiratory depression. Although the utilization of dexmedetomidine is associated with hypotension and bradycardia, both usually resolve without intervention. Thus, intravenous dexmedetomidine provides a further option as a short-term (<24 hours) primary sedative in mechanically ventilated adult patients in an intensive care setting and in non-intubated adult patients prior to and/or during surgical and other procedures.

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