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ADIS DRUG EVALUATION

Dexmedetomidine: A Review of Its Use for Sedation in the Intensive Care Setting

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Abstract Dexmedetomidine (Dexdor®) is a highly selective α_2-adrenoceptor agonist. It has sedative, analgesic and opioid-sparing effects and is suitable for short- and longer-term sedation in an intensive care setting. In the randomized, double-blind, multicentre MIDEX and PRODEX trials, longer-term sedation with dexmedetomidine was noninferior to midazolam and propofol in terms of time spent at the target sedation range, as well as being associated with a shorter time to extubation than midazolam or propofol, and a shorter duration of mechanical ventilation than midazolam. Patients receiving dexmedetomidine were also easier to rouse, more co-operative and better able to communicate than patients receiving midazolam or propofol. Dexmedetomidine had beneficial effects on delirium in some randomized, controlled trials (e.g. patients receiving dexmedetomidine were less likely to experience delirium than patients receiving midazolam, propofol or remifentanil and had more delirium- and coma-free days than patients receiving lorazepam). Intravenous dexmedetomidine had an acceptable tolerability profile; hypotension, hypertension and bradycardia were the most commonly reported adverse reactions. In conclusion, dexmedetomidine is an important option for sedation in the intensive care setting.

Dexmedetomidine for sedation in the intensive care setting: a summary

Highly selective α_2-adrenoceptor agonist with sedative, analgesic and opioid-sparing effects
Suitable for short- and longer-term sedation in an intensive care setting
Patients receiving dexmedetomidine are easier to rouse, more co-operative and better able to communicate versus patients receiving midazolam or propofol
Appears to have beneficial effects on delirium
Acceptable tolerability profile; most commonly associated with hypotension, hypertension and bradycardia

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1 Introduction

Sedation plays a key role in the management of agitation and anxiety in the intensive care setting [1]. The usual goal of sedation in the intensive care unit (ICU) is a calm, co-operative patient who is easy to rouse and who is able to communicate their needs, particularly for analgesia [2].

Guidelines recommend the use of dexmedetomidine, propofol and benzodiazepines (most commonly midazolam

and lorazepam) for sedation in an intensive care setting, and suggest that nonbenzodiazepine agents may be preferred over benzodiazepines [3]. Maintaining a light level of sedation in ICU patients is recommended, when possible, given that light sedation is associated with improved outcomes, including a shorter duration of ventilation and a shorter ICU stay [3].

Dexmedetomidine (Dexdor®) is approved in the EU for the sedation of adult patients in the ICU who require a sedation level not deeper than arousal in response to verbal stimulation [4]. This article reviews the efficacy and tolerability of dexmedetomidine for sedation of adult patients in an intensive care setting, as well as summarizing its pharmacological properties. The use of dexmedetomidine in procedural sedation has been reviewed previously [5] and is beyond the scope of this review.

2 Pharmacological Properties

2.1 Pharmacodynamic Profile

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist with a broad range of pharmacological properties, reflecting the extensive distribution of α_2-receptors throughout the body [6, 7].

The sedative effects of dexmedetomidine are well established [6]. Dose-dependent sedation was seen in healthy volunteers receiving intravenous boluses of dexmedetomidine 0.25–2 μg/kg [8], and the sedative effects of dexmedetomidine infusion were shown in both healthy volunteers [9–11] and intensive care patients [12–15] (see also Sect. 3). A Ramsay sedation score (RSS) of ≥3 was generally achieved when the plasma dexmedetomidine concentration was 0.2–0.3 ng/mL, and the sedation level appeared to plateau at a plasma dexmedetomidine concentration of 0.7–1.25 ng/mL (corresponding to a maintenance infusion rate of 0.337–0.7 μg/kg/h) [7]. Dexmedetomidine induces sleep by decreasing the firing of noradrenergic locus ceruleus neurons in the brain stem and activating endogenous non-rapid eye movement sleep-promoting pathways [16]; it produces a state closely resembling physiological stage 2 sleep [17]. Dexmedetomidine recipients could be easily roused to participate in testing [11] and co-operate with procedures [13].

Dexmedetomidine had analgesic effects in healthy volunteers [9, 11] and an opioid-sparing effect in patients in an intensive care setting [13] (see also Sect. 3). The analgesic effect appears to be exerted at the spinal cord level and supraspinal sites, as well as through nonspinal mechanisms [6].

Dexmedetomidine has sympatholytic activity [9, 18–20]. Significant ($p < 0.05$) reductions from baseline in plasma noradrenaline (norepinephrine) and/or adrenaline (epinephrine) levels were seen in healthy volunteers [9, 18, 19] or postoperative patients [20] receiving dexmedetomidine.

Dexmedetomidine has a biphasic effect on blood pressure (BP), with decreased BP seen at low dexmedetomidine concentrations and increased BP seen at high dexmedetomidine concentrations [9, 18]. Reductions in BP were commonly seen in healthy volunteers [9, 18, 19, 21, 22] and intensive care patients [12, 15, 18, 23–26] who received dexmedetomidine (see also Sect. 4). For example, in critically ill patients requiring sedation for >24 h who received infusion of dexmedetomidine 0.2–0.7 μg/kg/h (i.e. within the recommended dose range; Sect. 5) without a loading dose, mean systolic BP decreased by 16 % within 2 h [12]. In healthy volunteers, BP was increased above baseline when the plasma dexmedetomidine concentration was >3.2 ng/mL [9]. Indeed, a transient increase in BP was seen with high bolus doses of dexmedetomidine (1 or 2 μg/kg administered over 2 or 5 min) in healthy volunteers [18, 22] and in some intensive care patients receiving dexmedetomidine (loading dose of 1 μg/kg followed by a maintenance infusion of 0.2–0.7 μg/kg/h) [24, 25, 27]. This initial increase in BP was thought to be mediated by peripheral vasoconstriction, which occurred before the onset of the sympatholytic activity associated with dexmedetomidine [18].

Heart rate also decreases as the dexmedetomidine concentration increases [9, 18]; a reduction in heart rate was seen until the plasma dexmedetomidine concentration was 3.2–5.1 ng/mL, after which it remained stable [9]. Reductions in heart rate were commonly seen in healthy volunteers [9, 18, 19, 21, 22] and intensive care patients [12, 13, 15, 23, 24, 26] who received dexmedetomidine (see also Sect. 4). For example, in critically ill patients who received infusion of dexmedetomidine 0.2–0.7 μg/kg/h without a loading dose, mean heart rate decreased by 21 % within 12 h [12].

Dexmedetomidine was not associated with rebound hypertension or tachycardia after discontinuation [12, 13, 15, 25, 26]. For example, minimal changes in systolic BP and heart rate were seen following abrupt cessation of dexmedetomidine in critically ill patients [12].

Memory was preserved in healthy volunteers receiving lower doses of dexmedetomidine (target plasma concentrations of ≤0.7 ng/mL) [9], although some amnesia was seen in other studies [11, 13, 25] (e.g. intensive care patients receiving dexmedetomidine could generally recall the length of their ICU stay, but not the duration of mechanical ventilation [13]). Unlike propofol, dexmedetomidine preserved cognitive function in intensive care patients [28, 29]. For example, in the randomized, double-blind, crossover ANIST trial, a significant ($p < 0.001$ vs.

baseline) increase (i.e. improvement) in the mean adjusted overall Adapted Cognitive Exam score was seen in intensive care patients with dexmedetomidine, whereas a significant ($p = 0.018$ vs. baseline) decrease was seen with propofol, with the between-treatment difference significantly favouring dexmedetomidine (19.19; $p < 0.001$) [28].

In general, dexmedetomidine did not result in clinically significant respiratory depression in healthy volunteers [8–11] or intensive care patients [24, 25, 27, 30].

2.2 Pharmacokinetic Profile

Intravenous dexmedetomidine 0.2–1.4 μg/kg/h demonstrated linear pharmacokinetics [4, 31], and no accumulation was seen when dexmedetomidine was infused for up to 14 days [4]. Dexmedetomidine pharmacokinetics were adequately described by a two-compartment disposition model [4, 20, 32]. Dexmedetomidine had a rapid distribution phase in healthy volunteers, with a central estimate of the distribution half-life of ≈6 min [4]. In patients in the intensive care setting receiving dexmedetomidine for >24 h, dexmedetomidine had a volume of distribution at steady state of ≈93 L, plasma clearance of ≈43 L/h and terminal elimination half-life of ≈1.5 h [4]. Plasma protein binding of dexmedetomidine was 94 % (predominantly to albumin) [4].

Dexmedetomidine undergoes extensive hepatic metabolism [4]. Initial metabolites are formed via direct *N*-glucuronidation, direct *N*-methylation and oxidation catalysed by cytochrome P450 (CYP) enzymes (CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19) [4]. The pharmacological activity of these metabolites is negligible [4]. Nine days after the intravenous administration of radiolabelled dexmedetomidine, 95 and 4 % of radioactivity was recovered in the urine and faeces, respectively [4]. Less than <1 % of the dose was recovered in the urine as parent drug [4].

Given that dexmedetomidine is extensively metabolized in the liver, it should be used with caution in patients with hepatic impairment and a reduction in the maintenance dosage should be considered [4]. The pharmacokinetics of dexmedetomidine were not altered to a clinically relevant extent based on age or gender or in patients with severe renal impairment [4, 33], and no dosage adjustment is needed in the elderly or in patients with renal impairment [4]. Population pharmacokinetic analysis suggested a strong correlation between bodyweight and the clearance of dexmedetomidine [31]. Race did not appear to affect the pharmacokinetics of dexmedetomidine, with no significant differences seen between Caucasian and South Korean or Japanese subjects [7, 34]. Dexmedetomidine clearance did not significantly differ between normal, intermediate and slow CYP2A6 metabolizers [35].

2.3 Potential Drug Interactions

Enhanced effects (sedative, anaesthetic, cardiorespiratory effects) may be seen with the coadministration of dexmedetomidine and anaesthetics, sedatives, hypnotics or opioids (e.g. isoflurane, propofol, alfentanil, midazolam) [4, 36, 37]. For example, dexmedetomidine induced a dose-dependent reduction in the minimum alveolar anaesthetic concentration of isoflurane; the estimated isoflurane concentration required to suppress the motor response in 50 % of healthy volunteers was significantly ($p < 0.0001$) lower in low-dose or high-dose dexmedetomidine recipients than in placebo recipients (0.72 and 0.52 vs. 1.05 %) [36]. Dexmedetomidine also reduced the propofol concentration required for sedation and for suppression of the motor response by ≈65–80 % and ≈40 %, respectively [37]. Although pharmacokinetic interactions were not observed between dexmedetomidine and isoflurane, propofol, alfentanil or midazolam, a reduction in the dosage of dexmedetomidine or the coadministered agent may be needed because of pharmacodynamic interactions [4, 36, 37].

It is possible that the hypotensive and bradycardic effects of dexmedetomidine may be enhanced when other agents with these effects (e.g. β-blockers) are coadministered [4]. A modest enhancement of hypotensive and bradycardic effects was seen when dexmedetomidine and esmolol were coadministered [7].

In vitro, dexmedetomidine inhibited CYP enzymes (including CYP2B6) and induced CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4 [4]. Therefore, there is potential for interaction between dexmedetomidine and substrates with dominant CYP2B6 metabolism (e.g. bupropion, artemisinin, pethidine, methadone); other interactions cannot be excluded [4].

3 Therapeutic Efficacy

This section focuses on larger (n ≥ 70), randomized controlled trials primarily designed to examine the efficacy of short-term sedation (Sect. 3.1) and longer-term sedation (Sect. 3.2) with dexmedetomidine in the intensive care setting. Smaller ($n = 12$–30) studies demonstrating the efficacy of sedation with dexmedetomidine in the intensive care setting are not discussed [12–15]. Trials primarily designed to examine the effect of dexmedetomidine on delirium are also briefly discussed (Sect. 3.3). In some trials, a loading dose of dexmedetomidine was administered prior to the maintenance infusion; it should be noted

that use of a loading dose is not recommended in clinical practice (Sect. 5).

3.1 Short-Term Sedation

3.1.1 Comparisons with Placebo

The efficacy of short-term sedation with dexmedetomidine was compared with that of placebo in randomized, double-blind, multicentre trials [24, 25]. One of these trials reported results from four UK centres included in a European study [24]. Trials included postoperative patients in an intensive care setting who were expected to require ≥6 h of mechanical ventilation; sedation was continued for ≥6 h postextubation with a maximum duration of infusion of 24 h [24, 25]. Patients were randomized to receive dexmedetomidine ($n = 203$ [25] and 47 [24]) or placebo ($n = 198$ [25] and 51 [24]). Following administration of a loading dose of dexmedetomidine 1 μg/kg, the maintenance infusion (0.2–0.7 μg/kg/h) was titrated to the sedation target [24, 25]. Where specified, the primary endpoint was the amount of propofol required to maintain a RSS of ≥3 during ventilation [25]. Efficacy analyses were conducted in the intent-to-treat population [24, 25].

In terms of rescue sedation, mean doses of propofol (71.6 vs. 513.2 mg; $p < 0.001$) [25] and midazolam (4.9 vs. 23.7 μg/kg/h; $p < 0.0001$) [24] required to maintain target sedation during ventilation were significantly lower in patients receiving dexmedetomidine than those receiving placebo. The mean propofol requirement following extubation was also significantly lower with dexmedetomidine than with placebo (8.4 vs. 46.6 mg; $p = 0.028$) [25]. Sixty percent of dexmedetomidine recipients required no propofol, whereas 76 % of placebo recipients received propofol [25].

In terms of rescue analgesia, patients receiving dexmedetomidine had significantly lower mean morphine requirements during intubation (4.1 vs. 8.5 mg; $p < 0.001$ [25] and 11.2 vs. 21.5 μg/kg/h; $p < 0.0006$ [24]) and following extubation (1.3 vs. 4.1 mg; $p < 0.001$ [25] and 4.8 vs. 5.8 μg/kg/h; $p < 0.027$ [24]) than patients receiving placebo.

Nursing assessments revealed that patients receiving dexmedetomidine were significantly ($p < 0.001$) easier to manage than patients receiving placebo [25].

3.1.2 Comparisons with Propofol and Clonidine

The efficacy of short-term sedation (<24 h) with dexmedetomidine was compared with that of propofol in randomized, open-label, multicentre [27] or single-centre [38] trials and with that of clonidine in a randomized, double-blind, multicentre trial [26]. These studies were conducted in ventilated patients in an intensive care setting who had undergone coronary artery bypass graft surgery [27, 38] or surgical, medical or trauma patients who required ventilation and light to moderate sedation for <24 h [26]. Treatment regimen details are shown in Table 1. Primary endpoints included the efficacy of sedation [27] and the need for additional sedation [26].

In the multicentre study, the mean RSS score during ventilation did not significantly differ between dexmedetomidine and propofol recipients (Table 1) [27]. In terms of rescue sedation, 11 % of dexmedetomidine recipients received propofol during ventilation (Table 1). Significantly ($p < 0.001$) more dexmedetomidine than propofol recipients required no morphine during ventilation (72 vs. 37 %) or in the 6 h following extubation (69 vs. 24 %). The median time to extubation is shown in Table 1 [27].

In the single-centre study, the level of sedation was significantly higher with propofol than with dexmedetomidine (Table 1), with no significant between-group difference in midazolam or morphine requirements during the ICU stay [38]. There was no significant between-group difference in the duration of mechanical ventilation or ICU stay (Table 1). Overall, patient-rated outcomes (e.g. comfort level, pain, ability to sleep) did not significantly differ between patients receiving dexmedetomidine and those receiving propofol [38].

Significantly fewer dexmedetomidine than clonidine recipients required additional sedation with diazepam [8 of 35 (23 %) vs. 14 of 35 (40 %) patients; Table 1] [26]. In addition, the median diazepam dose was significantly lower in dexmedetomidine than clonidine recipients (8.5 vs. 15 mg; $p = 0.043$). Significantly more RSS observations were in the target sedation range with dexmedetomidine than with clonidine (Table 1) [26].

3.2 Longer-Term Sedation

A randomized, double-blind, multicentre pilot study compared the efficacy of dexmedetomidine with that of standard care (midazolam or propofol) in medical and surgical patients ($n = 85$) requiring mechanical ventilation who needed sedation for ≥24 h and had an expected ICU stay of ≥48 h [39]. This pilot study found that dexmedetomidine was suitable for maintaining light to moderate sedation [Richmond Agitation-Sedation Scale (RASS) of 0 to −3], but not deep sedation (RASS of −4 or less) [39]. Given the availability of subsequent, larger trials (MIDEX [40], PRODEX [40], SEDCOM [41]) comparing the efficacy of dexmedetomidine with that of midazolam or propofol for maintaining light to moderate sedation, this pilot study [39] is not discussed further.

Table 1 Sedative effects of dexmedetomidine in the intensive care setting

Study (study name)	Treatment[a]	No. of pts[b]	Time at target sedation range[c]	RSS score[d]	Rescue sedation[e] (% of pts)	Duration of mechanical ventilation[f]	Median time to extubation	Median duration of ICU stay
Short-term sedation								
Corbett et al. [38]	DEX 0.2–0.7 μg/kg/h	43		3.67*		10.2 h		23.0 h
	PRO 5–75 μg/kg/min	46		4.00		8.97 h		23.0 h
Herr et al. [27]	DEX 0.2–0.7 μg/kg/h	148		4.5[g]	11		410 min	
	PRO[h]	147		4.7[g]			462 min	
Srivastava et al. [26]	DEX 0.2–0.7 μg/kg/h	35	86[†]	3.20	23[†g]		19 h	
	CLO 1–2 μg/kg/h	35	62	3.37	40[g]		18 h	
Longer-term sedation								
Jakob et al. [40] (MIDEX)	DEX 0.2–1.4 μg/kg/h	249	60.7[g,i]		43.8	123 h[‡g]	101 h[‡‡]	211 h
	MID 0.03–0.2 mg/kg/h	251	56.6[g]		45.4	164 h[g]	147 h	243 h
Jakob et al. [40] (PRODEX)	DEX 0.2–1.4 μg/kg/h	251	64.6[g,i]		72.5	97 h[g]	69 h*	164 h
	PRO 0.3–4.0 mg/kg/h	247	64.7[g]		64.4	118 h[g]	93 h	185 h
Riker et al. [41] (SEDCOM)	DEX 0.2–1.4 μg/kg/h	244	77.3[g]		63[‡]		3.7 days[‡‡]	5.9 days
	MID 0.02–0.1 mg/kg/h	122	75.1[g]		49		5.6 days	7.6 days

Trials included surgical or medical pts [41], surgical, medical or trauma pts [26, 40] or post-coronary artery bypass graft pts [27, 38]

CLO clonidine, *DEX* dexmedetomidine, *ICU* intensive care unit, *ITT* intent-to-treat, *MID* midazolam, *PRO* propofol, *pts* patients, *RASS* Richmond Agitation-Sedation Scale, *RSS* Ramsay sedation scale

* $p < 0.05$ vs. PRO; † $p < 0.05$ vs. CLO; ‡ $p < 0.05$, ‡‡ $p \leq 0.01$ vs. MID

[a] Study drugs were titrated to achieve target sedation levels. A loading dose of DEX 0.7 μg/kg [26] or 1 μg/kg [27, 38] was administered in three trials. Optional loading doses of DEX ≤1 μg/kg or MID ≤0.5 mg/kg were administered to 8.2 and 7.4 % of pts in SEDCOM [41]

[b] No. of pts in the ITT [26, 27, 38, 40] or modified ITT [41] population; efficacy endpoints were assessed in these populations unless stated otherwise

[c] The % of the total time spent at the target sedation range [RASS score of 0 to −3 (without the need for rescue therapy) [40] or +1 to −2 [41]], or the proportion of observations within the target sedation range (RSS score of 3–4) [26]

[d] Median [38] or mean [26, 27]

[e] Rescue sedation comprised PRO in MIDEX and MID in PRODEX [40], PRO [27], MID [41] or diazepam [26]

[f] Median [40] or mean [38]

[g] Primary endpoint

[h] A PRO dose was not specified; investigators were told to follow their usual practice

[i] DEX was noninferior to MID in MIDEX and to PRO in PRODEX; this endpoint was assessed in the per-protocol population

MIDEX [40], PRODEX [40] and SEDCOM [41] were randomized, double-blind, multicentre trials conducted in medical or surgical patients [41] or in medical, surgical or trauma patients [40]. Patients required ventilation and light to moderate sedation, and were expected to require sedation for ≥24 h [40] or had an anticipated ventilation and sedation duration of ≥3 days after the start of the study drug [41]. Treatment regimen details are shown in Table 1; study drugs were administered until extubation or for a maximum 14 [40] or 30 [41] days. Primary endpoints included the proportion of time at the target sedation range (RASS score of 0 to −3 [40] or +1 to −2 [41], without rescue medication [40]) and the duration of mechanical ventilation [40].

In the MIDEX and PRODEX trials, dexmedetomidine was noninferior to midazolam and propofol in terms of time at target sedation without rescue medication [40] (Table 1). The time at target sedation did not significantly differ between dexmedetomidine and midazolam recipients in the SEDCOM trial [41] (Table 1).

The time to extubation was significantly shorter with dexmedetomidine than with midazolam in the MIDEX [40] and SEDCOM [41] trials (Table 1). There was no significant difference between dexmedetomidine and midazolam recipients in the length of ICU stay [40, 41], although the duration of mechanical ventilation was significantly shorter with dexmedetomidine than with midazolam in MIDEX [40] (Table 1). The median duration of study drug treatment was significantly shorter with dexmedetomidine than with midazolam in SEDCOM (3.5 vs. 4.1 days; $p = 0.01$), although significantly more dexmedetomidine than midazolam recipients required rescue sedation with midazolam (Table 1) [41]. The

median duration of study drug treatment did not significantly differ between dexmedetomidine and midazolam recipients in MIDEX (42 vs. 43 h) [40].

In PRODEX, the time to extubation was significantly shorter with dexmedetomidine than with propofol, with no significant between-group difference in the duration of mechanical ventilation or the length of ICU stay (Table 1) [40]. The median duration of study drug treatment was significantly shorter with dexmedetomidine than with propofol (42 vs. 47 h; $p < 0.001$) [40].

Study drug discontinuation occurred in 24 % of dexmedetomidine recipients and 20 % of midazolam recipients in MIDEX and in 28 % of dexmedetomidine recipients and 23 % of propofol recipients in PRODEX [40]. Significantly ($p < 0.05$) more patients receiving dexmedetomidine versus midazolam (9 vs. 4 %) or propofol (14 vs. 5 %) discontinued treatment because of lack of efficacy in these studies [40].

In both MIDEX and PRODEX, patients receiving dexmedetomidine were significantly ($p < 0.001$) more rousable, more co-operative and better able to communicate than patients receiving midazolam or propofol [40].

3.3 Effects on Delirium

This section focuses on trials primarily designed to compare the effect of dexmedetomidine on delirium with that of lorazepam [42], morphine [43], remifentanil [44] and propofol or midazolam [45]. Two trials (MENDS [42] and DEXCOM [43]) were of randomized, double-blind, multicentre design and two trials were of randomized, open-label, single-centre design [44, 45]. Trials included post-cardiac surgery patients [43–45] or surgical and medical patients [42] who required ventilation and sedation in an intensive care setting. Treatment regimen details are shown in Table 2. Primary endpoints included the incidence of postoperative delirium [43–45] and the number of delirium- and coma-free days [42].

Over a 12-day study period in the MENDS trial, patients receiving dexmedetomidine had significantly more delirium-

Table 2 Effect of dexmedetomidine on delirium in the intensive care setting

Study (study name)	Treatment[a]	No. of pts[b]	Delirium[c] (%)	Duration of delirium[d] (days)	Median no. of delirium- and coma-free days	Time to extubation[d]	Duration of ICU stay[d]
Comparison with LOR							
Pandharipande et al. [42] (MENDS)	DEX 0.15–1.5 μg/kg/h	52	79		7**[e]		7.5 days
	LOR 1–10 mg/h	51	82		3[e]		9 days
Comparison with MOR							
Shehabi et al. [43] (DEXCOM)	DEX 0.1–0.7 μg/kg/h	152	8.6[e]	2*		14 h*	45 h
	MOR 10–70 μg/kg/h	147	15.0[e]	5		15 h	45 h
Comparison with REM							
Park et al. [44]	DEX 0.2–0.8 μg/kg/h	67	9.0*[e]	3.5		22.7 h	67.7 h
	REM 1–2.5 mg/h	75	22.7[e]	3.8		18.6 h	61.3 h
Comparison with MID or PRO							
Maldonado et al. [45]	DEX 0.2–0.7 μg/kg/h	30	3[†‡e]	2.0		11.9 h[f]	1.9 days
	MID 0.5–2 mg/h	30	50[e]	5.4		12.7 h[f]	3.0 days
	PRO 25–50 μg/kg/min	30	50[e]	3.1		11.1 h[f]	3.0 days

Trials included post-cardiac surgery pts [43–45] or surgical and medical pts [42]

DEX dexmedetomidine, *ICU* intensive care unit, *ITT* intent-to-treat, *LOR* lorazepam, *MID* midazolam, *MOR* morphine, *PRO* propofol, *pts* patients, *REM* remifentanil

* $p < 0.05$, ** $p = 0.01$ vs. comparator; † $p < 0.001$ vs. MID; ‡ $p < 0.001$ vs. PRO

[a] Study drugs were titrated to achieve target sedation levels. A loading dose of DEX 0.4 μg/kg [45] or 0.5 μg/kg [44] was administered in two trials

[b] No. of pts in the ITT [42, 44], modified ITT [43] and per-protocol [45] populations

[c] Delirium was assessed using the Confusion Assessment Method for Intensive Care [41–44] or diagnostic criteria from the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (text revision) [45]. The delirium endpoint refers to the prevalence of delirium over the 12-day study period [42] or the proportion of pts developing delirium within 3 [44, 45] or 5 [43] days of surgery

[d] Median [42, 43] or mean [44, 45]

[e] Primary endpoint

[f] Intubation time

and coma-free days than patients receiving lorazepam (Table 2) [42]. The median number of coma-free days was significantly greater with dexmedetomidine than with lorazepam (10 vs. 8 days; $p < 0.001$), with no significant between-group difference in the median number of delirium-free days (9 vs. 7 days). The prevalence of delirium did not significantly differ between dexmedetomidine and lorazepam recipients (Table 2), although the prevalence of delirium and coma (87 vs. 98 %; $p = 0.03$) or coma (63 vs. 92 %; $p < 0.001$) was significantly lower with dexmedetomidine than with lorazepam [42]. Significantly ($p < 0.05$) more time was spent with the RASS score within one point of nurse (80 vs. 67 %) or physician (67 vs. 55 %) sedation targets with dexmedetomidine versus lorazepam [42]. There was no significant difference between dexmedetomidine and lorazepam recipients in the length of ICU stay (Table 2) or the median number of ventilator-free days over a 28-day study period (22 vs. 18 days) [42].

A prespecified subgroup analysis of MENDS found that the mean number of delirium- and coma-free days was significantly longer with dexmedetomidine than with lorazepam in patients with sepsis (6.1 vs. 2.9 days; $p = 0.005$) [$n = 63$], but not in those without sepsis (6 vs. 5.5 days) [$n = 39$] [46].

In the DEXCOM study, the incidence of delirium did not significantly differ between dexmedetomidine and morphine recipients, although the duration of delirium was significantly shorter with dexmedetomidine than with morphine (Table 2) [43]. The time to extubation was significantly shorter with dexmedetomidine than with morphine, although there was no significant between-group difference in the length of ICU stay (Table 2) [43]. The proportion of patients who maintained a Motor Activity Assessment Scale score within the target sedation range did not significantly differ between dexmedetomidine and morphine recipients (75.2 vs. 79.6 %) [43].

Patients receiving dexmedetomidine were significantly less likely than those receiving remifentanil to experience delirium (Table 2) [44]. There were no significant differences between dexmedetomidine and remifentanil recipients in the length of delirium or ICU stay, or the time to extubation (Table 2) [44].

The incidence of delirium was significantly lower with dexmedetomidine than with midazolam or propofol, although the duration of delirium did not significantly differ between treatment groups (Table 2). There were no significant between-group differences in the duration of ICU stay or intubation (Table 2) [45].

Delirium was also assessed as a secondary endpoint in the SEDCOM trial [41]. In this trial, the prevalence of delirium was significantly lower with dexmedetomidine than with midazolam (54 vs. 77 %; $p < 0.001$) and the mean number of delirium-free days was significantly higher in patients receiving dexmedetomidine than in those receiving midazolam (2.5 vs. 1.7 days; $p = 0.002$) [41].

4 Tolerability and Safety

Intravenous dexmedetomidine had an acceptable tolerability profile when used for sedation in the intensive care setting. The most commonly reported adverse reactions in patients receiving dexmedetomidine were hypotension, hypertension and bradycardia (occurring in approximately 25, 15 and 13 % of patients, respectively), and the most commonly reported serious adverse reactions were hypotension and bradycardia (reported in 1.7 and 0.9 % of patients), according to a pooled analysis of clinical trial data [4].

Short-term sedation with dexmedetomidine was associated with a significantly higher incidence of hypotension (30 vs. 10 %; $p < 0.001$) and bradycardia (9 vs. 2 %; $p = 0.003$) than placebo, although hypertension occurred in significantly fewer dexmedetomidine than placebo recipients (12 vs. 23 %; $p = 0.005$) [25]. Patients receiving short-term sedation with dexmedetomidine were significantly less likely than patients receiving clonidine to experience hypotension (9 vs. 31 %; $p = 0.01$), with no significant between-group difference in the incidence of bradycardia (11 vs. 9 %) [26].

With longer-term sedation in the MIDEX trial, hypotension and bradycardia occurred in significantly more dexmedetomidine than midazolam recipients, whereas sinus tachycardia occurred in significantly fewer dexmedetomidine than midazolam recipients (Fig. 1) [40]. In the PRODEX trial, patients receiving dexmedetomidine were significantly more likely than patients receiving propofol to experience sinus tachycardia, but significantly less likely to experience pleural effusion, with no significant between-group difference in the incidence of hypotension or bradycardia (Fig. 1) [40]. In the SEDCOM trial, dexmedetomidine recipients were significantly more likely than midazolam recipients to experience bradycardia (42 vs. 19 %; $p < 0.001$) and significantly less likely to experience tachycardia (25 vs. 44 %; $p < 0.001$), with no significant between-group difference in the incidence of hypotension (56 vs. 56 %) or hypertension (43 vs. 44 %) [41].

Episodes of hypotension in patients receiving dexmedetomidine generally resolved with no treatment, with a change in positioning or with the administration of fluids or vasoactive agents; titration, interruption or discontinuation of dexmedetomidine was required in some patients [24, 25, 27]. In the SEDCOM trial, there was no significant difference between dexmedetomidine and midazolam recipients in the incidence of hypotension

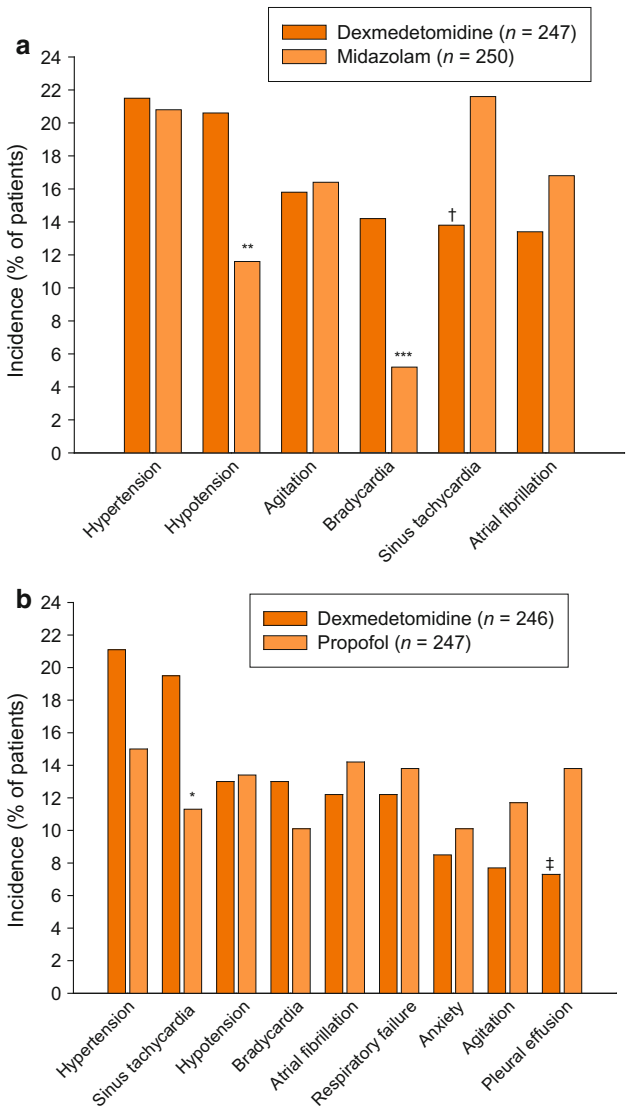

Fig. 1 Tolerability of longer-term sedation with intravenous dexmedetomidine in the intensive care setting. Results of trials comparing dexmedetomidine with **a** midazolam (MIDEX trial) and **b** propofol (PRODEX trial) [40]. Shown are adverse events occurring in >10 % of patients in any treatment group over 45 days of follow-up. *$p < 0.05$, **$p < 0.01$, *** $p < 0.001$ vs. dexmedetomidine; †$p < 0.05$ vs. midazolam; ‡$p < 0.05$ vs. propofol

requiring intervention (28 vs. 27 %) [41]. Bradycardia usually resolved spontaneously or with the administration of drugs such as atropine [24, 25]; pacing or discontinuation of the dexmedetomidine infusion was required in some patients [24]. The proportion of patients with bradycardia requiring intervention did not significantly differ between dexmedetomidine and midazolam recipients in the SEDCOM trial (5 vs. 0.8 %) [41].

During 48 h of follow-up in MIDEX, the incidence of neurocognitive adverse events did not significantly differ between dexmedetomidine and midazolam recipients (28.7 vs. 26.8 % of patients); agitation occurred in 15.0 versus 14.4 %, anxiety occurred in 7.7 versus 4.0 % and delirium occurred in 7.7 versus 7.6 % [40]. In PRODEX, patients receiving dexmedetomidine were significantly less likely than those receiving propofol to experience neurocognitive adverse events (18.3 vs. 28.7 % of patients; $p = 0.008$); agitation occurred in 7.3 versus 11.3 %, anxiety occurred in 8.1 versus 8.1 % and delirium occurred in 2.8 versus 6.9 % [40]. There was no significant difference between dexmedetomidine and midazolam in the proportion of patients requiring treatment for neurocognitive adverse events (25.5 vs. 22.4 %), although such treatment was needed in significantly fewer dexmedetomidine than propofol recipients (15.0 vs. 24.7 %; $p = 0.009$) [40].

Where reported, mortality did not significantly differ between patients receiving dexmedetomidine and those receiving comparator agents [38, 40–43]. For example, 45-day mortality was 22.2 % in patients receiving dexmedetomidine and 20.3 % in patients receiving standard care (midazolam or propofol) in the MIDEX and PRODEX trials [40]. In the SEDCOM trial, 30-day mortality did not significantly differ between dexmedetomidine and midazolam recipients (22.5 vs. 25.4 %) [41], and there was no significant difference between dexmedetomidine and lorazepam recipients in 28-day mortality (17 vs. 27 %) or the risk of death at 12 months in the MENDS trial [42]. However, in the MENDS subgroup analysis, 28-day mortality was significantly lower with dexmedetomidine than with lorazepam in patients with sepsis (16 vs. 41 %; $p = 0.03$), with no significant between-group difference in patients without sepsis (19 vs. 5 %) [46]. It should be noted that none of these trials were powered to examine mortality [38, 40–43, 46].

Dexmedetomidine overdose in clinical trials and the postmarketing setting has been associated with adverse reactions such as bradycardia, hypotension, oversedation, somnolence and cardiac arrest, although none of the overdose episodes resulted in death [4]. In patients who are symptomatic following dexmedetomidine overdose, the infusion should be reduced or stopped and symptoms should be treated as appropriate [4].

5 Dosage and Administration

Dexmedetomidine (Dexdor®) is approved in the EU for sedation of adult patients in the ICU who require a sedation level not deeper than arousal in response to verbal stimulation (RASS score of 0 to −3) [4]. Patients who are already intubated and sedated may be switched to dexmedetomidine with an initial infusion rate of 0.7 μg/kg/h, which may then be titrated within a range of 0.2–1.4 μg/kg/h in order to achieve the desired level of sedation [4]. After adjusting the dexmedetomidine dose, it may take up to 1 h to reach a new steady-state sedation level. The maximum dexmedetomidine dose of 1.4 μg/kg/h should not be exceeded; patients who do

not achieve an adequate level of sedation with the maximum dexmedetomidine dose should be switched to an alternative sedative agent. Use of a dexmedetomidine loading dose is not recommended [4].

In the EU, the use of dexmedetomidine is contraindicated in patients with advanced (grade 2 or 3) heart block (unless paced), uncontrolled hypotension or acute cerebrovascular conditions [4].

Local prescribing information should be consulted for further information concerning contraindications, special warnings and precautions for use related to dexmedetomidine.

6 Place of Dexmedetomidine for Sedation in the Intensive Care Setting

Dexmedetomidine provides effective light to moderate sedation in an intensive care setting (Sect. 3). Dexmedetomidine is not considered suitable for use in patients requiring continuous deep sedation [4]. Dexmedetomidine has analgesic and opioid-sparing activity and is not associated with clinically significant respiratory depression, meaning it does not interfere with ventilator weaning and extubation [27]. Patients receiving dexmedetomidine are easily roused, meaning they are able to cooperate with nursing and radiological procedures within the intensive care setting, and wake-up trials to assess outcomes can be easily conducted [6, 27].

Propofol and benzodiazepines are γ-aminobutyric acid (GABA) receptor agonists; these agents have sedative, anxiolytic, amnestic and anticonvulsant effects, lack analgesic activity and are associated with respiratory depression and hypotension [1, 3, 47]. Tolerance and delayed emergence from sedation may also occur with prolonged use of benzodiazepines [3]. Propofol has a quick onset and offset of action, allowing rapid awakening [3, 47]; both propofol and midazolam need to be discontinued to achieve arousal.

Longer-term sedation with dexmedetomidine was non-inferior to midazolam and propofol in the MIDEX and PRODEX trials (Sect. 3.2). Dexmedetomidine was also associated with a shorter time to extubation than midazolam (in MIDEX and SEDCOM) and propofol (in PRODEX), and a shorter duration of mechanical ventilation than midazolam in MIDEX. Patients receiving dexmedetomidine were easier to rouse, more co-operative and better able to communicate than those receiving midazolam or propofol in the MIDEX and PRODEX trials.

Significantly more dexmedetomidine than midazolam or propofol recipients discontinued treatment because of lack of efficacy in MIDEX and PRODEX (Sect. 3.2). It has been stated that with a maximum dexmedetomidine dose of 1.4 μg/kg/h, lack of efficacy can be expected in approximately one out of eight to ten patients [40]. Possible reasons for interpatient variability in dexmedetomidine response include patient characteristics (e.g. ethnicity), differences in drug pharmacokinetics seen in critically ill patients and genetic polymorphisms in metabolism and receptor response [48].

Historically, clonidine has been the α_2-adrenoceptor agonist most commonly used for sedation in Europe [2]. Disadvantages of clonidine include its long duration of action and the potential for rebound hypertension following discontinuation [2]. Dexmedetomidine has greater selectivity for α_2-adrenoceptors than clonidine [49]. Patients receiving short-term sedation with dexmedetomidine were more likely to achieve target sedation and were less likely to need additional sedation or to experience hypotension than patients receiving clonidine (Sects. 3.1.2, 4).

Dexmedetomidine has a predictable cardiovascular profile and may be associated with hypotension and bradycardia (Sect. 2.1, 4). Although hypotension and bradycardia are common adverse events, episodes are often not clinically significant and require no intervention [41–43]. When intervention is required, hypotension and bradycardia can be managed with dexmedetomidine dose reduction or with the administration of fluids and/or appropriate medication (e.g. vasoconstrictors for hypotension). All patients should have continuous cardiac monitoring during dexmedetomidine infusion [4]. The EU summary of product characteristics states that dexmedetomidine is not suitable for use in patients with severe cardiovascular instability, and should be used with caution in patients with pre-existing bradycardia [4].

In several of the studies discussed in Sect. 3, a loading dose of dexmedetomidine was administered prior to the maintenance infusion. However, use of a loading dose is not recommended in clinical practice (Sect. 5), as it has been associated with an increased incidence of adverse reactions [4], including loading-dose hypotension [15, 24, 27] and hypertension [24, 25, 27] (see Sect. 2.1).

In the EU, dexmedetomidine is currently only approved for use in adults [4]. Retrospective data suggest a role for sedation with dexmedetomidine in paediatric patients, although concerns have been raised about rebound and withdrawal phenomena following longer-term sedation [50–56]; prospective data in the intensive care setting are currently limited [57].

A European cost-minimization analysis, based on the MIDEX and PRODEX trials, predicted that total ICU costs would be lower with dexmedetomidine than with midazolam or propofol [58]. Dexmedetomidine was associated with lower resource utilization compared with the pooled comparator population, mainly reflecting a significantly ($p = 0.0003$) shorter time to extubation, thus offsetting the higher acquisition cost of dexmedetomidine [58].

Delirium, which affects up to 80 % of mechanically ventilated ICU patients, has a deleterious effect on outcomes and is associated with substantial costs [3]. Risk factors for delirium include pre-existing dementia, history of alcoholism or hypertension, severe illness at baseline and coma, with benzodiazepine use also implicated [3].

In several trials, dexmedetomidine appeared to lessen the risk of delirium. For example, patients receiving dexmedetomidine were significantly less likely to experience delirium than patients receiving midazolam (Sect. 3.3) and had significantly more delirium- and coma-free days than patients receiving lorazepam (Sect. 3.3). The incidence of delirium was also significantly lower with dexmedetomidine than with propofol or remifentanil, and the duration of delirium was significantly shorter with dexmedetomidine than with morphine (Sect. 3.3).

Possible explanations for the beneficial effects of dexmedetomidine on delirium include that it has intrinsic delirium-sparing properties (e.g. its high selectivity for α_2-adrenoceptors, its lack of anticholinergic effects, its promotion of a physiological sleep-like state), and that it reduces requirements for other agents with greater potential for delirium (e.g. opioids and GABAergic agents) [45, 59].

Haloperidol is commonly used to treat delirium in the ICU [59]. Results of a small pilot trial found that dexmedetomidine was more effective than haloperidol for facilitating extubation in delirious, agitated, intubated patients in an intensive care setting [60]. In addition, a small observational study found that dexmedetomidine facilitated weaning from ventilation in agitated, mechanically ventilated patients [61].

In conclusion, dexmedetomidine is an important option for sedation in the intensive care setting.

Data selection sources: Relevant medical literature (including published and unpublished data) on dexmedetomidine was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 25 May 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Dexmedetomidine, Precedex, Dexdor, MPV?1440, sedati*, critical*, intensive care
Study selection: Studies in patients receiving dexmedetomidine for sedation in an intensive care setting. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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