

Dexmedetomidine: its use in intensive care medicine and anaesthesia

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Key points

- Dexmedetomidine provides a unique quality of conscious sedation which resembles natural sleep.
- Its administration does not result in respiratory depression.
- It is licensed for intensive care sedation in the UK.
- Its use as a perioperative sedative is growing.
- The use of dexmedetomidine as a sole agent for general anaesthesia in specific circumstances has been reported.

Dexmedetomidine is a relatively new drug to the UK having been launched in October 2011 with marketing authorization for sedation of adult intensive care unit (ICU) patients only. Despite this, its unique pharmacological profile has led to its unlicensed use in a number of areas of anaesthetic and critical care practice where evidence for its efficacy is mounting.

Drug actions

Dexmedetomidine is the S-enantiomer of the veterinary sedative medetomidine. It is a highly selective α_2 -adrenoceptor agonist demonstrating an $\alpha_2:\alpha_1$ selectivity ratio of 1620:1. This makes it eight times more selective for the α_2 -adrenoceptor than clonidine.

Sedation and anxiolysis

These properties are mediated via agonism of α_2 -adrenoceptors primarily in the locus coeruleus of the pons where it results in

dose-dependent inhibition of norepinephrine release. It is postulated that this results in disinhibition of the ventrolateral pre-optic nucleus which then releases inhibitory neurotransmitters. This pathway is part of the complex circuitry governing natural sleep, resulting in a quality of sedation with dexmedetomidine which more closely resembles normal physiological sleep than the more familiar GABA-ergic sedatives (propofol and the benzodiazepines). This sedation is characterized by preserved muscle tone and ventilation, by spontaneous and evoked movements, and by awakening by external stimuli. Once roused, patients are cooperative and can typically obey simple instructions. Once the external stimulus is discontinued, patients resume the previous level of sedation. Electroencephalogram studies have further confirmed that the sedative effects of dexmedetomidine mimic stage 2 non-rapid eye movement sleep.¹

Analgesia

It is likely that dexmedetomidine exerts effects at various sites in the pain pathway, but its main site of action is at the level of the spinal cord where stimulation of α_2 -receptors in the substantia gelatinosa of the dorsal horn reduces the release of nociceptive neurotransmitters such as substance P.

Effects on organ systems

The cardiovascular effects of the drug are biphasic (Fig. 1). At higher rates of infusion, such as during administration of a loading dose, the predominant effect is hypertension due to activation of α_{2B} receptors on vascular smooth muscle. This is superseded by hypotension and bradycardia as a result of the centrally mediated inhibition of sympathetic outflow. Case reports of bradycardia leading to asystole after loading dose administration of the drug in conjunction with multiple other

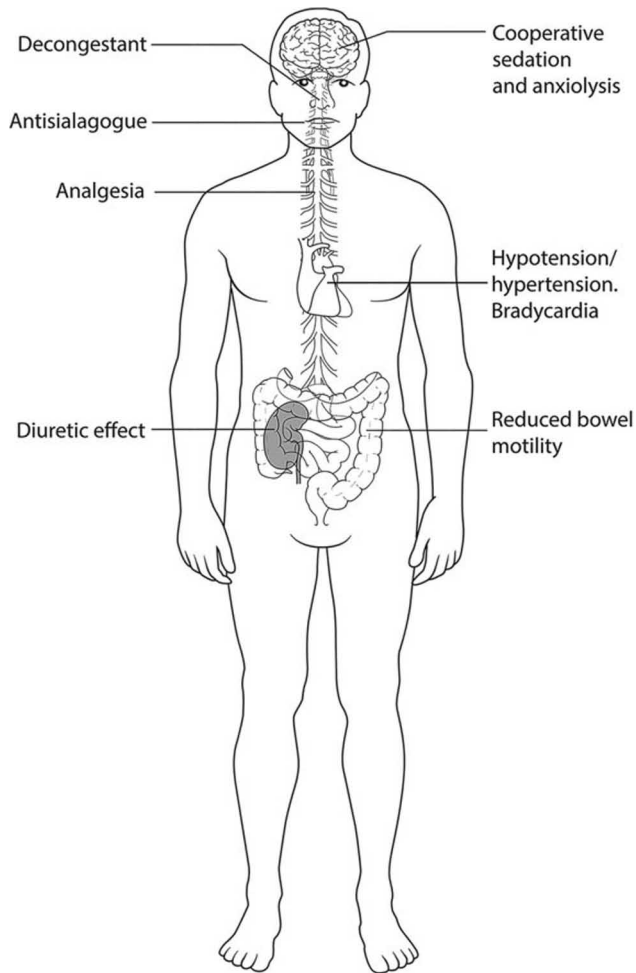


Fig 1 Effects of dexmedetomidine on organ systems.

anaesthetic agents can be found in the literature.² Cardiovascular adverse effects associated with dexmedetomidine may be expected to be more pronounced in hypovolaemic patients, in those with diabetes mellitus or chronic hypertension, in the elderly and in those with high vagal tone.

A defining feature of the sedative action of dexmedetomidine is its minimal effect on ventilation, even when given in doses 10 times the maximum recommended.³ In addition, MRI studies have shown that the airway remains patent during dexmedetomidine sedation.

Owing to actions on peripheral α_2 -adrenoceptors, dexmedetomidine also has decongestant and antisialagogue effects. It may theoretically reduce bowel motility, although to our knowledge, there have been no reports of associated complications. Dexmedetomidine suppresses shivering, possibly due to agonism of α_{2B} -receptors in the hypothalamus. It exerts a diuretic effect by inhibiting the action of ADH at the collecting duct.

Despite its imidazole structure, dexmedetomidine has not been found to cause any clinically significant adrenal suppression.

Pharmacokinetics

Administration is possible via multiple routes, with a bioavailability of 16% when given orally, 65% nasally, and 82% buccally. It is 94% protein bound with the unbound drug freely crossing

the blood–brain barrier to exert its central effects, with a distribution half-life of 6 min. It undergoes glucuronidation, hydroxylation, and N-methylation in the liver to inactive metabolites which are then renally excreted. Hepatic impairment therefore should prompt a dose reduction due to decreased protein binding and metabolism, while renal impairment and renal replacement therapy requires no dose adjustment. It has a terminal elimination half-life of ~2 h with clearance estimated at 39 litre h^{-1} . Its steady-state volume of distribution (118 litres) is increased in patients with low plasma albumin concentration, prolonging the terminal half-life and context-sensitive half-time in such patients.⁴

Pharmaceutical information

Dexdor[®], the formulation of dexmedetomidine marketed in the UK by Orion Pharma (UK) Limited, is presented as a clear, colourless solution containing 100 $\mu g ml^{-1}$ concentrate. It is available in ampoules of 2 ml and vials of 2, 4, and 10 ml. It is diluted before administration to a concentration of 4 $\mu g ml^{-1}$ using glucose 5% or sodium chloride 0.9% and can be administered centrally or peripherally.

Contraindications

Uncontrolled hypotension and second- or third-degree heart block (unless a pacemaker is fitted) may potentially be worsened by administration of dexmedetomidine. The presence of ‘acute cerebrovascular conditions’ is also considered a contraindication as research in animals has shown a decrease in cerebral blood flow with dexmedetomidine. However, human studies have demonstrated a maintenance of flow-metabolism coupling with decreased rate of metabolic consumption in the brain matching the decreased cerebral blood flow.⁵

Sedation in the ICU

Dexmedetomidine is indicated for patients requiring a sedation level not deeper than arousal in response to verbal stimulation [corresponding to Richmond Agitation-Sedation Scale⁶ (RASS) 0 to -3; Table 1]. It is not suitable for patients requiring deep sedation.

Two phase III multicentre, randomized, double-blind trials⁷ compared dexmedetomidine for the sedation of intubated patients with the established sedatives, propofol (PRODEX) and midazolam (MIDEX). Dexmedetomidine was found to be as effective as propofol and midazolam in maintaining the target level of light to moderate sedation. The median duration of mechanical ventilation was significantly shorter with dexmedetomidine than with midazolam, but not when compared with propofol. No difference in ICU length of stay, hospital length of stay, or mortality was seen with 45 day follow-up.

In keeping with its unique mechanism of action, patients receiving dexmedetomidine were found to be more rousable, more cooperative, and better able to communicate their pain than those receiving the other sedatives. There was, however, more hypotension and bradycardia with dexmedetomidine when compared with midazolam, although with no increase in the rate of drug discontinuation due to adverse effects. The rates of hypotension and bradycardia with dexmedetomidine and propofol were comparable. Drug discontinuation due to lack of efficacy was higher with dexmedetomidine and the authors state that with the current maximum dose, lack of efficacy can be expected in ~1 in every 8 to 10 patients.⁷

Table 1 The Richmond Agitation-Sedation Scale.⁶ Dexmedetomidine is indicated for patients requiring sedation levels corresponding to levels 0 to -3 as shaded

Points	Classification	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour towards staff
+2	Agitated	Frequent non-purposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (>10 s) awakening, with eye contact, to voice
-2	Light sedation	Briefly (<10 s) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unrousable	No response to voice or physical stimulation

A recent Cochrane review⁸ supported the finding of reduced duration of mechanical ventilation with dexmedetomidine sedation, and also found a reduced ICU length of stay.

Potential indications

While non-inferiority to established sedatives for the licensed indication is proven, most UK ICUs currently reserve this drug for clinical situations in which they feel dexmedetomidine will provide additional benefits. This is in-keeping with the Intensive Care Society's position that 'the [sedative] agents chosen should be individualized to the patient's requirements, characteristics and the clinical situation'.⁹ While robust large trial evidence for these indications is not available, clinical experience of the use of dexmedetomidine with an application of its specific pharmacological properties suggest the following indications.

As a bridge to extubation

Dexmedetomidine does not cause respiratory depression or airway compromise. Patients sedated with it are more cooperative, communicative, and better able to follow commands than with other agents. It also depresses the gag reflex and improves tracheal tolerance when compared with other sedatives.⁹ This therapeutic profile makes it suitable for continuing infusion through the period of extubation in patients who deteriorate once sedatives are discontinued (e.g. the agitated patient), allowing for a smooth and non-combative extubation. Conversion of failed to successful extubation with the introduction of dexmedetomidine has been demonstrated in small trials.

While remifentanyl, as an ultra-short-acting opioid, is also sometimes used as a bridge to extubation, dexmedetomidine sedation can be continued post-extubation with less potential for respiratory depression or airway obstruction.

As an alternative sedative

Where propofol sedation is contraindicated (e.g. due to hypertriglyceridaemia) but in whom the delayed extubation associated with midazolam would be potentially detrimental.

Where the clinician feels an α_2 -agonist would be beneficial

Where the clinician feels an α_2 -agonist would be beneficial (e.g. sedation or drug withdrawal) but in whom clonidine is not efficacious. The improved specificity of dexmedetomidine for the α_2 -receptor makes it a more effective sedative than clonidine.

Patients at particular risk of critical care delirium

SEDCOM,¹⁰ a phase IV trial comparing dexmedetomidine and midazolam for light sedation, found a reduction in the

prevalence and duration of delirium in the dexmedetomidine group (and again found a significantly shorter time to extubation in this group). This reduction in delirium confirms findings from previous trials (although not a universal finding)⁸ and has led to guidance from the Society of Critical Care Medicine¹¹ recommending dexmedetomidine be used for sedation of patients with delirium not related to benzodiazepine or alcohol withdrawal in preference to benzodiazepines.

Where sedation is required to tolerate non-invasive ventilation in the ICU

Lack of respiratory depression and provision of 'rousable sedation' might make it particularly suitable for such patients. Small trial evidence of its efficacy in this situation is available.

There is early interest in a possible benefit of dexmedetomidine sedation in patients with sepsis via attenuation of immunosuppression.

Barriers to use on ICU, including pharmacoeconomic analysis

The frequency of the use of dexmedetomidine is anecdotally much lower than the other sedatives, with many units reserving it for the above clinical situations where it may be specifically indicated. This is likely to be due to a combination of factors. First, dexmedetomidine provides a novel, 'conscious sedation', unlike that of the other sedatives, with which critical care staff may be less familiar. In addition, the acquisition costs of the drug are higher than other agents—dexmedetomidine sedation of a 70 kg patient at the dose range of 0.2–1.4 $\mu\text{g kg}^{-1} \text{h}^{-1}$ for 24 h would cost £26–184. This compares with sedation of a 70 kg patient with propofol at the dose range of 0.3–4 $\text{mg kg}^{-1} \text{h}^{-1}$, which would have an up-front drug cost of £10–130 (costs and dose ranges as listed in the British National Formulary, March 2015). However, on the basis of the marketing company's cost-minimization analysis exploring costs associated with drug preparation, management of adverse events, co-prescribed medicines, and reduced costs associated with earlier extubation, the Scottish Medicines Consortium considers the economic case for the use of dexmedetomidine to be demonstrated.¹²

Drug administration

The dexmedetomidine infusion is begun at an infusion rate of 0.7 $\mu\text{g kg}^{-1} \text{h}^{-1}$ and is then adjusted according to response within the dose range 0.2–1.4 $\mu\text{g kg}^{-1} \text{h}^{-1}$. In contrast to its use in anaesthesia, it is recommended that no loading dose is given when used for sedation in the ICU. After dose adjustment, a new steady-

state sedation level may not be reached for up to 1 h. Many ICUs have protocols in place to allow nurses to bolus sedation when indicated, but it is important to note that dexmedetomidine should not be administered in this way. There is no published experience with infusions lasting >14 days.

A discontinuation syndrome manifest as rebound agitation, hypertension, and tachycardia is recognized after prolonged clonidine infusion and has occasionally been reported with dexmedetomidine.⁵ When stopping the drug, patients should be monitored for symptoms and if apparent should prompt a more gradual dose reduction.

Dexmedetomidine in anaesthetic practice

Although unlicensed for use other than for intensive care sedation in the UK, in the USA, dexmedetomidine is approved for sedation of non-intubated patients before and/or during surgical and other procedures.

The recommended dosing regimens when using dexmedetomidine for periprocedural sedation in the USA are described below.

A loading infusion of 1 $\mu\text{g kg}^{-1}$ over 10 min

A reduced loading infusion of 0.5 $\mu\text{g kg}^{-1}$ over 10 min is recommended for patients over 65 years of age and when less invasive procedures are to be undertaken (e.g. ophthalmic).

A maintenance infusion

This is generally initiated at 0.6 $\mu\text{g kg}^{-1} \text{h}^{-1}$ and titrated to the desired clinical effect between doses of 0.2 and 1.0 $\mu\text{g kg}^{-1} \text{h}^{-1}$. Maintenance infusion at 0.7 $\mu\text{g kg}^{-1} \text{h}^{-1}$ is advised when performing awake fiberoptic intubation until the tracheal tube is secured.

A reduction in the loading and maintenance dose are recommended when administering the drug to patients with hepatic impairment. Dexmedetomidine enhances the pharmacodynamic effects of other sedatives, anaesthetics, hypnotics, and opioids and concomitant use therefore should also prompt a dose reduction. Similarly, if a patient is being converted to dexmedetomidine from another sedative, a loading dose may not be necessary.

Perioperative use

Sedative premedication

Its anxiolytic, sedative, sympatholytic, and antisialagogue properties, along with a lack of respiratory depression make dexmedetomidine suitable for premedication. The drug also acts as an anaesthetic-sparing agent and obtunds the pressor response to intubation. Its versatility in route of administration is an advantage in paediatric premedication where intranasal administration of 1 $\mu\text{g kg}^{-1}$ dexmedetomidine was shown to be as effective as midazolam 0.5 mg kg^{-1} orally, with modest haemodynamic effects.¹³

Anaesthetic and opioid-sparing agent

Dexmedetomidine decreases anaesthetic requirements and is opioid sparing. These properties are particularly useful in certain patient populations where the respiratory-depressant properties of opioids may be particularly detrimental, such as in bariatric surgery.

Sympatholysis

A Cochrane review in 2009¹⁴ examined the theoretical benefits of α -agonists in obtunding the perioperative stress-induced increase in sympathetic activity, and thereby reducing cardiac complications of surgery. The authors found that perioperative

α_2 -agonists reduced mortality and myocardial ischaemia, with the greatest benefit seen in patients undergoing vascular surgery. There was, however, an increase in perioperative hypotension and bradycardia with drug administration. Overall, the data available to the authors were insufficient to make firm conclusions about the safety and efficacy of perioperative α_2 -agonists and further studies were called for.

Continuous infusion of dexmedetomidine throughout the extubation period has been used for emergence smoothing. The drug also offers effective prevention and treatment of emergence phenomena.

Postoperative analgesia

Postoperative dexmedetomidine infusions have been used to supplement other forms of analgesia in patients in whom opioid-induced respiratory depression would be potentially deleterious. A small randomized controlled trial of thoracic surgical patients found less supplemental epidural opioid was needed in the group who also received an i.v. dexmedetomidine infusion.

Neuroanaesthesia

Dexmedetomidine is routinely used in our centre for neurosurgical procedures requiring intraoperative patient cooperation, that is, awake craniotomy for supratentorial tumour resection or deep brain stimulator implantation. It does not suppress epileptiform activity in patients undergoing electrocorticography and so is useful in epilepsy surgery.

Dexmedetomidine administration has no effect on intracranial pressure. Although there were initial concerns that it may reduce cerebral blood flow leading to ischaemia, multiple studies have demonstrated a matched reduction in cerebral blood flow and cerebral metabolic rate.⁵ It does not affect somatosensory-evoked potentials or motor-evoked potentials and so may be a useful anaesthetic-sparing agent and analgesic supplement in scoliosis surgery.

Experimental studies show dexmedetomidine has neuroprotective effects in hypoxic-ischaemic and traumatic brain injury models. This neuroprotection appears to be afforded by the action of the drug on α_{2A} -receptors and at imidazoline receptors. The clinical relevance of these findings is yet to be fully evaluated.

Sedation for invasive procedures

Awake fiberoptic intubation

A recently published Cochrane review¹⁵ examined the use of dexmedetomidine for awake fiberoptic intubation. Owing to the heterogeneity of the available studies, they were unable to conduct a full meta-analysis. The review considered four randomized controlled trials examining dexmedetomidine given by bolus followed by infusion with controls of midazolam, fentanyl, propofol, and normal saline. They concluded that dexmedetomidine significantly reduced the participants discomfort with awake fiberoptic intubation compared with control groups. No significant differences were seen between the treatment and control groups in terms of airway obstruction, hypoxia, or cardiovascular adverse events. However, the authors note that these conclusions are based on weak evidence and they await the report of ongoing trials.

Many small randomized controlled trials have reported benefits when using dexmedetomidine for sedation for invasive procedures compared with standard techniques. Procedures investigated include radiological and gastrointestinal endoscopic procedures, awake carotid endarterectomy, shockwave lithotripsy, and dental procedures.

Sedation for non-invasive procedures in challenging patients

The pharmacotherapeutic properties of dexmedetomidine have led to its use for paediatric and adult sedation for radiological investigations. It is of particular use in patients in whom the respiratory-depressant effects of other sedatives should be minimized, for example, those with obstructive sleep apnoea or an anterior mediastinal mass.

Regional anaesthesia adjuncts

A limited number of studies have shown a prolongation of regional nerve block when dexmedetomidine was added to the local anaesthetic. Clonidine remains popular as an adjunct to local anaesthetic for caudal epidural in children. The use of dexmedetomidine has been described as efficacious in providing prolonged neuraxial analgesia, although its superiority to clonidine for this indication has not been proven.

General anaesthesia single-agent case reports

There have been case reports of the use of dexmedetomidine as a sole agent for general anaesthesia. These patients required doses of 5–10 $\mu\text{g kg}^{-1} \text{h}^{-1}$ (5 to 10 times the maximum recommended for procedural sedation) to be adequately anaesthetized. The authors chose this technique in two of the cases due to the nature of the surgery; laser ablation of a tracheal stenosis, and a tracheal debridement with stenting and bronchopulmonary lavage. Dexmedetomidine allowed preservation of respiratory drive with easy maintenance of a patent airway (one patient required a chin lift). There was no haemodynamic compromise in this small group of patients.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at <https://access.oxfordjournals.org> by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/ceaccp_16.07.01.mp3.

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