Clinical application of dexmedetomidine

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Introduction

Dexmedetomidine is a highly selective and potent alpha₂-adrenoreceptor (AR) agonist offering dose-dependent sedation, anxiolysis and analgesia. It is a relatively new drug, approved for sedation for up to 24 hours in mechanically ventilated post-cardiac surgery patients. Yet, because of its unique drug profile, it has been increasingly studied and used in various clinical settings, albeit off label, with promising results. The purpose of this review is to discuss dexmedetomidine in terms of its pharmacokinetics and pharmacodynamics, and to focus on its various clinical applications. A PubMed search, using the keyword “dexmedetomidine”, identified approximately 1,000 articles, the earliest being animal studies published in 1988.

Dexmedetomidine is the dextro-stereoisomer and active ingredient of medetomidine, an agent used for many years in veterinary anaesthesia. It has a seven-to eight-fold higher affinity for the alpha₂-AR than clonidine. Alpha₂-ARs are found ubiquitously in the central, peripheral and autonomic nervous systems, as well as in vital organs and blood vessels. Receptor activation leads to inhibition of noradrenaline release or hyperpolarisation.

The distribution half-life of dexmedetomidine is about six minutes, and its terminal elimination half-life is approximately two hours. It is highly protein-bound (94%), but has no significant drug interactions with other highly protein-bound drugs. Its metabolites are inactive and excreted renally. It is recommended to reduce the dosage administered in patients with severe liver failure and end-stage renal disease. Oral bioavailability is poor, owing to an extensive first-pass effect. However, bioavailability of dexmedetomidine administered sublingually is high (84%), offering a potential role in paediatric sedation and premedication.

Sedation

The sedative effect of dexmedetomidine is exercised subcortically and mimics natural sleep. The area of the brain with the highest concentration of alpha₂-ARs is the locus coeruleus (LC) in the upper brainstem, which is responsible for arousal, sleep, anxiety, and withdrawal symptoms from drug addiction. It projects into two areas in the thalamus: the ventrolateral preoptic nucleus and the tuberomammillary nucleus.

When the alpha₂-AR is activated, it inhibits adenylyl cyclase. This results in the reduction of cAMP, with net efflux of K⁺ (through Ca²⁺-activated K⁺ channels) and inhibition of Ca²⁺ entry into nerve terminals. This hyperpolarises the neuron and suppresses the release of noradrenaline (NA) from the LC.

In the awake state (Figure 1), the release of NA from the LC inhibits the ventrolateral preoptic nucleus (VLPO). The VLPO, in turn, releases less γ-aminobutyric acid (GABA) and galanin to inhibit the tuberomammillary nucleus (TMN). The TMN is then free to release histamine, which binds to histamine receptors in the cortex and subcortical areas, producing the awake state.

During normal non-REM sleep or with alpha₂-receptor activation, reduced noradrenergic inhibitory control over the VLPO results in an increased release of GABA and galanin which, in turn, inhibits the TMN release of histamine into the cortex and subcortical areas. This final effect of reduced histamine receptor occupancy is thought to produce the hypnotic state.

The central hypnotic effect of dexmedetomidine, therefore, does not directly involve the GABA system and, consequently, does not cause cognitive impairment or disinhibition, as can propofol or benzodiazepines. Patients are calm and easily roused from sleep with good communication and performance of complex tasks, and they can then return to sleep.
The predominant effect of dexmedetomidine is hypotension mediated by central alpha2-receptors. Hypotension has been described in patients with pre-existing hypovolaemia. This usually occurs early and is also related to the loading dose. In most cases, it responds to a fluid bolus. Hypotension may also be more pronounced in diabetes mellitus and chronic hypertension, and in the elderly. The South African Society of Anaesthesiologists’ Acute Pain Guidelines, published in 2009, recommend that the loading dose of 1µg/kg be infused over 30 minutes.

Bradycardia and sinus arrest have been described, primarily in younger patients with high levels of vagal tone. The use of beta-blockade does not seem to increase the risk of bradycardia.

Dexmedetomidine is not recommended for use in patients diagnosed with advanced heart block or ventricular dysfunction.

**Respiratory effects**

Several studies have confirmed that dexmedetomine does not suppress respiratory function, even at high doses. The respiratory effects of dexmedetomidine have been compared with remifentanil in healthy volunteers using target controlled infusions of the two drugs (Figure 2). Remifentanil infusion reduced respiratory rate and minute ventilation and caused respiratory acidosis, as well as apnoic episodes. In the dexmedetomidine group, respiratory rate increased significantly and the overall apnoea/hypopnoea index significantly decreased. Patients also exhibited hypercapnoeic arousal. In response to a 5% CO2 mixture of inspired gas, patients exhibited partial awakening (as detected by Bispectral Index (BIS) monitoring) and hyperventilation.

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**Analgesia**

Analgesia is produced at spinal level in the dorsal horn, where dexmedetomidine reduces transmission of nociceptive signals, including substance P. It is not as potent as opioids, but is significantly opiate-sparing and may be particularly useful in neuropathic pain.

**Cardiovascular effects**

The haemodynamic effects of dexmedetomidine result from peripheral and central mechanisms.

The peripheral alpha2-receptors located on vascular smooth muscle mediate vasoconstriction. The initial response to rapid infusion of dexmedetomidine may, therefore, be transient hypertension. This has been shown when the recommended loading dose of 1µg/kg is given in less than 10 minutes.

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**Figure 1: Projection from the locus coeruleus: neurotransmitter release in the awake state and during non-REM sleep**

Walking

- Cortex & Subcortical areas
- Histamine
- TMN
- VLPO
- NA
- Locus Coeruleus

Non-REM Sleep

- Cortex & Subcortical areas
- Histamine
- TMN
- GABA
- VLPO
- NA
- Locus Coeruleus

The alpha2-receptor antagonist atipamezole reverses dexmedetomidine-induced sedation.

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**Figure 2: Peripheral cardiovascular effects of dexmedetomidine**

**Figure 3: Central cardiovascular effects of dexmedetomidine**
Dexmedetomidine is sympatholytic and can reduce the stress response to surgery. Animal studies have demonstrated the occurrence of natriuresis and diuresis. Dexmedetomidine is an imidazole agent but, unlike etomidate, it does not appear to inhibit steroidogenesis when used as an infusion for short-term sedation. Studies suggest that it may be neuroprotective by reducing circulating and brain levels of catecholamines and, possibly, by reducing levels of the excitotoxin glutamate implicated in cellular brain injury, particularly in subarachnoid haemorrhage. The MAC-sparing effect of dexmedetomidine in a dose-related manner has been shown.

Sedation in the ICU

The FDA limitations placed on the infusion duration and dose range of dexmedetomidine (0.2–0.7 µg/kg/hr) stem from the results of small, short duration studies. Dexmedetomidine has, however, been successfully administered for longer durations and at higher doses. In a study comparing dexmedetomidine with propofol for sedation in ICU, post-CABG patients receiving dexmedetomidine infusion achieved similar levels of sedation and had similar extubation times, but they required significantly less morphine, beta-blockers, antiemetics, nonsteroidal anti-inflammatory drugs, adrenaline, or high-dose diuretics. No ventricular tachycardia occurred in the dexmedetomidine sedated patients.

Table I: Comparison of endocrine and other effects of dexmedetomidine and propofol

|                     | Dexmedetomidine | Propofol |
|---------------------|-----------------|----------|
| adrenocorticotropic hormone and cortisol | unchanged | unchanged |
| cardiovascular       | heart rate decreased | blood pressure unchanged |
|                     | blood pressure unchanged | blood pressure unchanged |
| glucose             | unchanged | unchanged |
| insulin             | decreased | unchanged |
| IL-6                | Unchanged at baseline. Decreased during study, but not statistically significant. (Study not powered sufficiently; β error 0.8) | Unchanged at baseline |

Neurophysiological effects

The cerebral blood flow and cerebral metabolic requirement of oxygen (CMRO₂) are reduced. Cerebral autoregulation is preserved. The effect on intracranial pressure is not yet clear. The predominant effect on cerebral vessels is vasoconstriction. Studies suggest that it may be neuroprotective by reducing circulating and brain levels of catecholamines and, possibly, by reducing levels of the excitotoxin glutamate implicated in cellular brain injury, particularly in subarachnoid haemorrhage. The MAC-sparing effect of dexmedetomidine in a dose-related manner has been shown.

In one study, the median infusion time was 71 hours. Patients were monitored during the infusion and for 24 hours after abrupt cessation of sedation. There was a predictably modest reduction in heart rate and blood pressure in the first few hours of the infusion, with no evidence of cardiovascular rebound. Rebound hypertension is a well-described consequence of clonidine administration. More than half of the surviving patients were receiving dexmedetomidine during and after successful extubation, implying that weaning of sedative, as practised with other commonly used agents, is not necessary.

Studies have shown that patients receiving dexmedetomidine have significantly lower requirements of rescue sedatives. One study showed the dose of morphine was reduced by 50%, and that of midazolam by 80%.

Other studies have confirmed that, compared to benzodiazepines, patients administered dexmedetomidine had less delirium. This was demonstrated in the MENDS trial, comparing dexmedetomidine with lorazepam infusions for up to five days. More recently, the efficacy and safety
of dexmedetomidine and midazolam have been compared. Time in the target sedation range was similar in both groups, but the prevalence of delirium was more than 20% higher in the midazolam group. Patients in the dexmedetomidine group were also extubated almost two days earlier.12

The superiority of dexmedetomidine over haloperidol has also been demonstrated. Patients who could not be extubated because of delirium and agitation had significantly shortened time to extubation and length of ICU stay when administered dexmedetomidine infusion versus haloperidol infusions.17

Neurosurgery

Neuroanaesthetic goals aim to provide stable cerebral haemodynamics without sudden increases in intracranial pressure (ICP), during both intubation and extubation. Immediate postoperative neurological evaluation depends on a fast recovery. Opiates blunt responses to awakening and extubation, but can cause respiratory depression with increased \( P_{\text{a}}CO_2 \) and ICP.2

Tanskanen et al used dexmedetomidine as an adjuvant in patients undergoing supratentorial brain tumour surgery in a double-blinded randomised controlled trial. Patients were randomised to receive a continuous dexmedetomidine infusion (plasma target concentration 0.2 or 0.4 ng/ml) or a placebo infusion, and maintained with isoflurane and nitrous oxide in oxygen. The dexmedetomidine groups received fentanyl at 2 \( \mu \)g/kg at the induction of anaesthesia; the placebo group received 4 \( \mu \)g/kg at induction. Surgery time was similar in the three groups. They found that, in the dexmedetomidine group, extubation times were significantly shorter. At intubation (Figure 5), the heart rate increase was significantly lower in the two dexmedetomidine groups. At extubation, systolic blood pressure (SBP) increase was significantly lower in the higher plasma concentration dexmedetomidine group. There was no significant difference in \( P_{\text{a}}CO_2 \) among the groups during the study period.18

Dexmedetomidine may be an ideal agent for “functional neurosurgery”. This includes awakecraniotomy for the resection of tumours or epileptic foci in eloquent areas, and the implantation of deep brain stimulators (DBS) for Parkinson’s disease. The asleep-awake-asleep technique is currently used most widely. Dexmedetomidine has been successfully administered for both of these procedures.2,6

Dexmedetomidine does not interfere with neurophysiological monitors. It does not affect the basal ganglia, nor does it attenuate the symptoms of Parkinson’s disease, unlike GABA agonist agents, including propofol. Patients remain cooperative during cognitive testing and brain mapping. Ventilation is maintained2,6 and dexmedetomidine offers better haemodynamic stability,6 with reduced use of antihypertensive drugs, particularly during head pin insertion.19

Paediatrics

In the paediatric population, dexmedetomidine has been used for sedation in the ICU and procedural sedation, as a premedicant and as an anaesthetic adjunct.

In one study, 30 infants and children requiring mechanical ventilation in the ICU were randomised to receive either midazolam infusion (0.1 \( \mu \)g/kg/hour), low dose dexmedetomidine (0.25 \( \mu \)g/kg/hour), or high dose dexmedetomidine (0.5 \( \mu \)g/kg/hour). The sedation scores were similar in all three groups. All patients required morphine but, compared to the midazolam group, the high dose dexmedetomidine group needed significantly less rescue morphine. No patients in the study developed hypotension.20
Dexmedetomidine appears to be particularly valuable in non-invasive procedural sedation, such as magnetic resonance imaging (MRI), for example. This is more so than for invasive procedures, such as CVP insertion or gastroscopy, particularly when used as the sole agent. One study compared dexmedetomidine with midazolam in children undergoing MRI (Table II). The investigators randomised 80 patients for inclusion in either a dexmedetomidine group, or a midazolam group. The loading dose of the study drugs was administered for 10 minutes (dexmedetomidine 1 µg/kg, or midazolam 0.2 µg/kg), followed by a continuous infusion (dexmedetomidine 0.5 µg/kg/hr, or midazolam 6 µg/kg/min). Adequate sedation was achieved in 80% of the dexmedetomidine group and in 20% of the midazolam group. The requirement of rescue drugs (namely propofol and midazolam) was significantly lower and the onset of sedation was shorter in the dexmedetomidine group. Cardiovascular effects were minimal in both groups. Respiratory depression and apnoea were not observed in any of the children who received dexmedetomidine during the study.21

With respect to paediatric premedication, a recent randomised controlled trial aimed to evaluate whether intranasal dexmedetomidine is as effective as oral midazolam, which is currently most commonly used. There were no significant differences in parental separation acceptance and wake up behaviour score between the two groups. Patients in the dexmedetomidine group were significantly more sedated when they were separated from their parents (p < 0.001), and at induction.22

"Awake" fibre optic intubation

In patients with a difficult airway in whom awake fibre optic intubation (AFOI) is undertaken, the anaesthetic goals are to maintain a patent airway with spontaneous ventilation in order to avoid respiratory depression and pulmonary aspiration. At the same time, the patient must be comfortable enough not to resist the procedure. Dexmedetomidine appears to be an ideal sedative agent for fibre optic intubation; it also has the added benefit of creating a dry field as it is an antisialogogue.23 Several case reports and case series have been published.24 Some of these are particularly illustrative.

- An adult male with an epidural haematoma and a C-spine fracture had impaired consciousness. The patient was combative and would not tolerate topical anaesthesia or nerve blocks. He was loaded with dexmedetomidine 1µg/kg, followed by an infusion of dexmedetomidine. No haemodynamic adverse events were noted. He did not cough during the procedure and obeyed commands after intubation.24

- An adult male with a large thyroid tumour, in whom nerve block was not performed because of distorted anatomy, underwent an AFOI under dexmedetomidine sedation following preparation with midazolam, glycopyrrolate and topical local anaesthesia (Figure 6).24

Figure 6: Computed tomographic view of a large thyroid mass causing deviation of the trachea

|                     | Dexmedetomidine group | Midazolam group | p     |
|---------------------|-----------------------|-----------------|-------|
| sedation            | adequate in 80%       | adequate in 20% | < 0.001 |
| rescue drugs        | ✓                     | *                | < 0.001 |
| onset of sedation   | 19 minutes (mean)     | 35 minutes (mean) | < 0.001 |
| cardiovascular effects | mean arterial pressure and heart rate | in both groups, but by < 20% | not significant |
| respiratory effects | No apnoea or reduction in respiratory function | 3 patients desaturated |      |
repair of a lower limb fracture. After conscious sedation with a loading dose and continuous infusion of dexmedetomidine, his agitation abated and the clinicians performed superior laryngeal and glossopharyngeal nerve blocks. Excellent intubating conditions were achieved, the patient was haemodynamically stable and calm, and he obeyed commands after tracheal intubation. 24

- An adult female with squamous carcinoma of the tonsil presented with upper airway obstruction requiring urgent airway management. The initial plan was an awake tracheostomy. The airway was secured by AFOI using topical anaesthesia and dexmedetomidine. 25

Cardiac surgery

In a randomised controlled trial, 80 patients presenting for elective CABG were allocated to receive either a saline placebo or dexmedetomidine infusion during surgery. A fentanyl-based anaesthetic technique was used. Compared with placebo, dexmedetomidine decreased plasma noradrenaline concentrations by 90%, blunted the blood pressure response to intubation and surgery and decreased blood pressure variability and tachycardia, although there was an increased tendency towards hypotension. Dexmedetomidine decreased the need for beta blockers and additional doses of fentanyl, as well as the incidence of fentanyl-induced muscle rigidity. Postoperative shivering was reduced and diuresis increased. 26

Dexmedetomidine has been successfully used to manage patients with pulmonary hypertension undergoing mitral valve replacement, with reduction in pulmonary vascular resistance, pulmonary artery pressure and pulmonary capillary wedge pressures.

A meta-analysis concluded that the use of alpha2-adrenergic agonists reduced mortality and myocardial infarction following vascular surgery and that, during cardiac surgery, a reduction in ischaemia was observed that may also have effects on mortality and myocardial infarction. 1

Another meta-analysis showed that dexmedetomidine was associated with a trend towards improved cardiac outcomes in non-cardiac surgery. 27 However, an adequately powered study of non-fatal myocardial infarction (with a reported event rate of 5.3% in the control group) and an expected 25% reduction in events would require more than 4,000 patients in each arm of the study. 27

Bariatric surgery

The incidence of obesity is rising, as is the number of obese patients presenting for surgery. Obesity is associated with a difficult airway, increased aspiration risk and respiratory and cardiovascular comorbidities. The incidence of obstructive sleep apnoea is high and these patients can be exquisitely sensitive to the respiratory depressant effects of sedatives and opiates. Dexmedetomidine, in this situation, offers adequate pain relief with minimal respiratory depression.

In a US study, 20 patients (with an average body mass index of 54–61 kg/m²) undergoing open gastric bypass surgery were randomised to receive either fentanyl (0.5 µg/kg bolus, then 0.5 µg/kg/hour) or dexmedetomidine (0.5 µg/kg bolus, then 0.4 µg/kg/hour). End-tidal desflurane was adjusted to maintain the BIS at 45–50. During surgery, desflurane concentration decreased from 0.8 MAC in the fentanyl to 0.6 MAC in the dexmedetomidine group (Figure 7). Blood pressure and heart rate were significantly lower in the dexmedetomidine group. Time to extubation after desflurane was turned off was significantly shorter in the dexmedetomidine group. This group also had lower pain scores and significantly decreased morphine use. Other studies have shown similar outcomes. 28

Figure 7: End-tidal concentration of desflurane titrated to a BIS value of 45–50 using dexmedetomidine versus fentanyl
Other applications

The literature suggests other potential uses for dexmedetomidine, for example:

- As an adjunct in ENT anaesthesia for middle ear surgery and rhinoplasty.
- As an adjunct in the repair of aortic aneurysms.
- Management of withdrawal from benzodiazepines and opiates.
- Management of tetanus in ICU.
- Obstetric anaesthesia and labour analgesia.

Conclusion

Dexmedetomidine has a unique pharmacokinetic and -dynamic profile, and has been shown to be safe and effective in a wide spectrum of clinical settings. It is proving to be a valuable and versatile drug in anaesthesia and intensive care. Medication costs may presently appear prohibitive.

However, overall patient cost should be considered. Dexmedetomidine has been shown to reduce length of ICU stay, as well as the incidence of cognitive dysfunction and the duration of mechanical ventilation. The latter may conceivably decrease the risk of nosocomial infection and the need for tracheostomy. As an anaesthetic adjunct, dexmedetomidine has significant dose-sparing effects on volatile agents and the drugs used in total intravenous anaesthesia techniques and may, in turn, lead to more rapid recovery and shortened turnaround times.

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