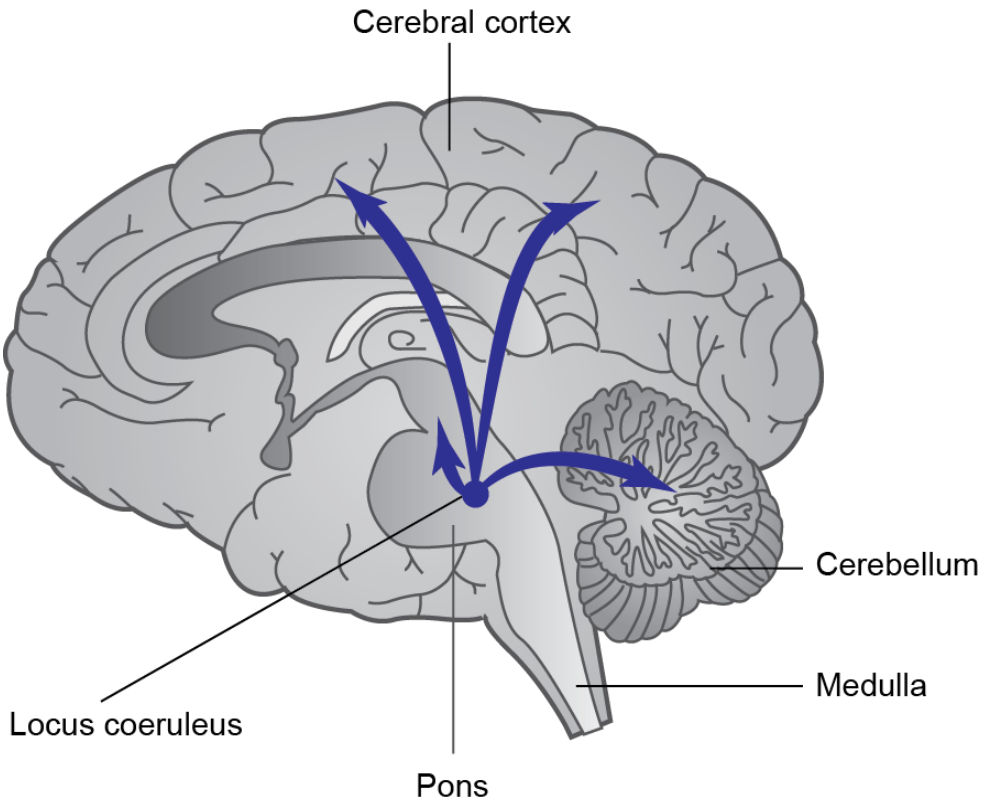
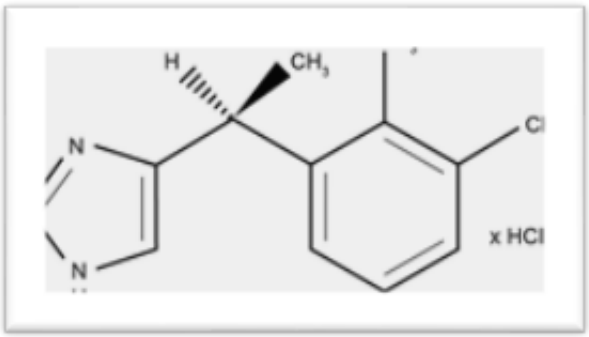
# DEXMEDETOMIDINE




## A Learning Resource for ICU Nursing Staff

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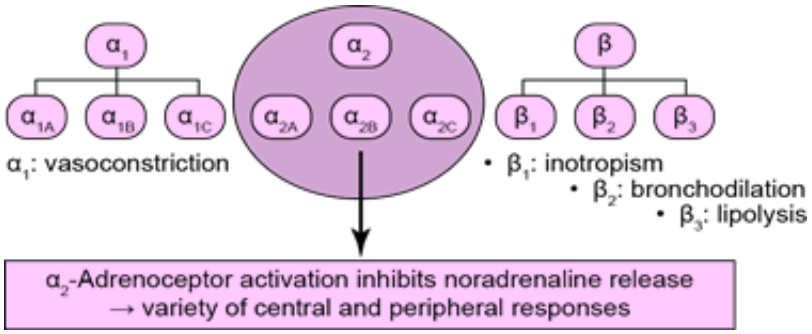
## Dexmedetomidine

Dexmedetomidine is an alpha-2 receptor agonist with a short half-life of about 2 hours. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings.

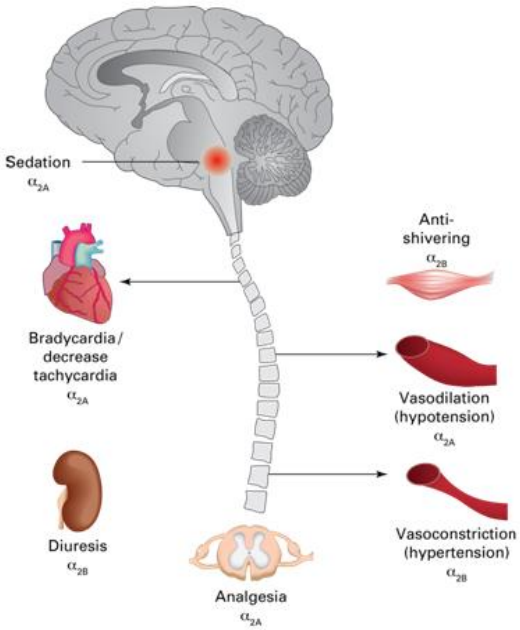



## How does it work?

It works by attaching to receptors in the brain called alpha-2 receptors and causes a reduction in the activity of the sympathetic nervous system which is involved in controlling people's anxiety, arousal and sleep as well the blood pressure and heart rate. By reducing the activity of the sympathetic nervous system, dexmedetomidine helps to make patients calm.

## Mode of action

The sedative action of dexmedetomidine is mediated through the inhibition of neuronal firing in the locus coeruleus in the brain stem.




Dexmedetomidine is used to as an alternative to sedate (calm or make sleepy) adult patients in hospital intensive care units.

It is used to bring about a relatively light level of sedation in which the patient can still respond to verbal stimulation (corresponding to a score of between 0 and -3 on the Richmond Agitation-Sedation Scale)

## Effects of dexmedetomidine

- Blood pressure and heart rate (central effect) ↓
- Blood pressure at high doses (peripheral vasoconstriction) ↑
- Cardiac output and oxygen need ↓
- Diuresis ↑
- Salivation ↓
- Intraocular pressure ↓
- Shivering ↓
- Insulin secretion ↓
- Secretory and motor function of gut ↓

## Contraindications

- Advanced heart block (grade 2 or 3) unless paced
- Uncontrolled hypertension
- Acute cerebrovascular conditions
- Severe neurological conditions
- Status epilepticus
- Malignant hyperthermia
- Pregnancy or breastfeeding
- Age < 18 yrs

## Dexmedetomidine is NOT suitable in the following

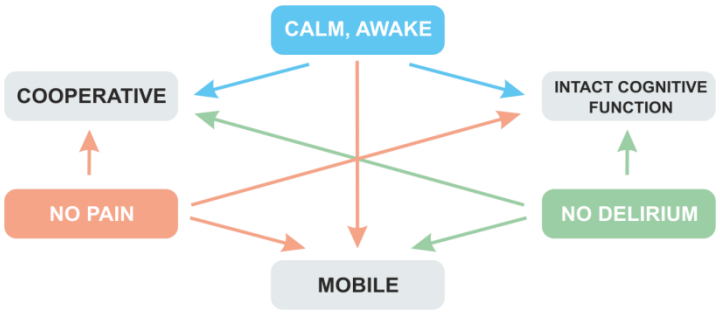
- Use in other environments is **not** recommended
- Patients requiring deep sedation (RASS -4 to -5)
- Patients with severe cardiovascular instability
- Dexmedetomidine does not appear to suppress seizure activity and should not be used as sole treatment in status eplipeticus
- Experience of the drug in severe neurological disorders such as head injury and after neurosurgery is limited and it should be used with caution here. Dexmedetomidine may reduce cerebral flow and intracranial pressure and this should be considered when selecting therapy

## Benefits

- **"Awake or conscious" sedation** – its unique mechanism of action, means that patients are found to be more rousable, more co-operative and better able to communicate their pain than others receiving other sedatives
- It is thought that the drug's effect may **involve natural sleep pathways**, which results in sedation that is **similar to normal physiological nonrapid eye movement** sleep

## Calm, alert and cooperative patient

A patient who is calm, alert and cooperative helps the ICU staff to improve patient management, including the assessment, treatment and prevention of pain, agitation and delirium. Consequently, the improved PAD management leads to improved short- and long-term outcomes of the patient




The target is to have a patient, who is calm, alert, pain-free and without delirium, allowing early mobilization and intact cognitive function.

## Dexmedetomidine is suitable for patients requiring a RASS target of -3 to 0 and in the following

### As an alternative sedative

- Where propofol is contraindicated e.g due to hypertriglyceridaemia
- Where the clinician feels an α2-agonist would be beneficial e.g sedation or drug withdrawal

### May be used as a bridge to extubation

- Dexmedetomidine does not cause respiratory depression or airway compromise. Patients sedated with it are more co-operative, 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
- So it may be **suitable for continuing the 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 has been demonstrated in small trials

**Where sedation is required to tolerate NIV in the ICU**

- Lack of respiratory depression and provision of 'rousable sedation' might make it particularly useful for such patients. **Suggest starting at lower dose e.g. 0.2µg/kg/hr**

**Patients at particular risk of critical care delirium**

- SEDCOM 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

## Dexmedetomidine presentation and safety considerations

**Presentation**

- Available in ready to administer bags containing 800mcg in 100ml providing a concentration of 8mcg/ml and administered via a volumetric infusion pump
- Also available in vials containing 400mcg in 4ml → 2 vials are added to 96ml saline to produce a concentration of 8mcg/ml and administered via a volumetric infusion pump
- If low-dose dexmedetomidine is required → 400mcg in 4ml is added to 46ml saline to produce concentration of 8mcg/ml and administered via a syringe driver

**Safety considerations**

- Dexmedetomidine must **not** be infused with other drugs → obtain a dedicated port
- Can be administered either centrally or peripherally
- Start infusion at **0.7µg**/kg/hr. However a lower initial dose should be considered in frail patients e.g. 0.4µg/kg/hr
- Dose is based on **actual** body weight. However, patients weighing > 100kg are limited to 100kg bodyweight dose range
- Use of a loading dose is **not** recommended and is associated with increased adverse reactions. Do **not** bolus dexmedetomidine
- Adjust the dose step-wise every 15 minutes as per infusion table. Refer to guidance on pages 7 and 8. Do **not** exceed the maximum dose of 1.4µg/kg/hr
- Steady state sedation level may not be reached for up to 1 hour.
- If patient fails to achieve an adequate level of sedation on maximum dose, dexmedetomidine should be switched to an alternative sedative agent.
- A discontinuation syndrome manifest as rebound agitation, hypertension and tachycardia is recognised after prolonged clonidine infusion and has occasionally been reported with dexmedetomidine. When stopping the drug, patients should be monitored for symptoms and if apparent should prompt a more **gradual dose** reduction

## Administration and preparation

**Preparation**

- 8 micrograms/ml solution should always be prescribed on the patient's drug kardex
- Preferably use pre-made 800micrograms/100ml bags and administer via a volumetric pump. If patients are on a very high rate, a 250ml or 500ml bag can be prepared. See **table 1** below for guidelines on preparing infusions
- Expiry time: 24 hours (store in fridge at 2 to 8 $^{o}$C if not administered immediately)
- Once the infusion bag is prepared → refer to **table 2** for appropriate infusion rates

**Table 1**

| **Volume of dexmedetomidine 100micrograms/ml and infusion fluid required to prepare 8 micrograms in 1ml infusion** | | |
|---|---|---|
| **Volume of dexmedetomidine 100 micrograms/ml concentrate for solution for infusion** | **Volume of diluent (sodium chloride 0.9% or glucose 5%)** | **Total volume of 8 micrograms/ml infusion** |
| 8ml | 92ml | 100ml |
| 20ml | 230ml | 250ml |
| 40ml | 460ml | 500ml |

**Table 2**

- For patients ≥ 65 years → commence infusion at 0.4 micrograms/kg/hr
- For patients ≤ 65 years → commence infusion at 0.7 micrograms/kg/hr

| **Infusion table: dexmedetomidine 8 micrograms/ml** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Weight (kg) | Dose (micrograms/kg/hour) | | | | | | | | | | | | |
| | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1.0** | **1.1** | **1.2** | **1.3** | **1.4** |
| **50** | 1.3 | 1.9 | **2.5** | 3.1 | 3.8 | 4.4 | 5.0 | 5.6 | 6.3 | 6.9 | 7.5 | 8.1 | 8.8 |
| **55** | 1.4 | 2.1 | **2.8** | 3.4 | 4.1 | 4.8 | 5.5 | 6.2 | 6.9 | 7.6 | 8.3 | 8.9 | 9.6 |
| **60** | 1.5 | 2.3 | **3.0** | 3.8 | 4.5 | 5.3 | 6.0 | 6.8 | 7.5 | 8.3 | 9.0 | 9.8 | 10.5 |
| **65** | 1.6 | 2.4 | **3.3** | 4.1 | 4.9 | 5.7 | 6.5 | 7.3 | 8.1 | 8.9 | 9.8 | 10.6 | 11.4 |
| **70** | 1.8 | 2.6 | **3.5** | 4.4 | 5.3 | 6.1 | 7.0 | 7.9 | 8.8 | 9.6 | 10.5 | 11.4 | 12.3 |
| **75** | 1.9 | 2.8 | **3.8** | 4.7 | 5.6 | 6.6 | 7.5 | 8.4 | 9.4 | 10.3 | 11.3 | 12.2 | 13.1 |
| **80** | 2.0 | 3.0 | **4.0** | 5.0 | 6.0 | 7.0 | 8.0 | 9.0 | 10.0 | 11.0 | 12.0 | 13.0 | 14.0 |
| **85** | 2.1 | 3.2 | **4.3** | 5.3 | 6.4 | 7.4 | 8.5 | 9.6 | 10.6 | 11.7 | 12.8 | 13.8 | 14.9 |
| **90** | 2.3 | 3.4 | **4.5** | 5.6 | 6.8 | 7.9 | 9.0 | 10.1 | 11.3 | 12.4 | 13.5 | 14.6 | 15.8 |
| **95** | 2.4 | 3.6 | **4.8** | 5.9 | 7.1 | 8.3 | 9.5 | 10.7 | 11.9 | 13.0 | 14.3 | 15.4 | 16.6 |
| **100** | 2.50 | 3.8 | **5.0** | 6.3 | 7.5 | 8.8 | 10.0 | 11.3 | 12.5 | 13.8 | 15.0 | 16.3 | 17.5 |

## Guidance on how to titrate dexmedetomidine 8micrograms/ml infusion

- Use a dedicated port – central or peripheral - do **not** administer any other drugs via this port
- Document baseline HR and BP before commencing dexmedetomidine → see table on page 8
- Using the appropriate bodyweight range, enter infusion rates in the boxes below and tick each box as the infusion rate is achieved → see table below
- Increase dexmedetomidine infusion rate **every 15 minutes** where BP and HR parameters allow
- Start reducing the propofol infusion rate as the BP and HR changes - **suggest titrating the propofol infusion 30 minutes** (if not sooner) after commencing dexmedetomidine. The aim is to reduce increased propofol requirements. However, a low dose background rate of propofol may still be needed and also intermittent boluses of propofol may still be needed PRN
- Noradrenaline infusion may be required for the transition. The noradrenaline infusion may need to be increased, decreased or even switched off during this time
- Try to avoid procedures that may stimulate HR/BP changes during the first couple of hours
- Bradycardia can be associated with dexmedetomidine – if bradycardia occurs **i.e. heart rate < 45/min → reduce the infusion rate by 2ml** and treat with glycopyrolate as per protocol
- Dexmedetomidine should **not** be abruptly discontinued as this may cause rebound hypertension and/or agitation. The infusion rate should be gradually tapered off.
- Dexmedetomidine can be continued following extubation – and the infusion rate can be gradually tapered off as appropriate. Low-dose dexmedetomidine may also be considered in the patient requiring NIV
- Complete table below as infusion rates are titrated. Closely monitor the patient's BP and HR and observe the patient for signs of increasing wakefulness → target RASS -1 to +1

| HR before commencing infusion _____ BP/MAP _____ | Time | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dexmedetomidine infusion rates for kg BW | | | | | | | | | | | | |
| Increase dexmedetmodine infusion every 15mins & tick √ box when infusion rate achieved | | | | | | | | | | | | |
| Start reducing propofol by 2ml at 30mins, then reduce by 2ml every 15mins & tick box √ to confirm | | | | | | | | | | | | |

**Start dexmedetomidine infusion as per protocol**

↓

Increase dexmedetomidine step-wise every 15 minutes → observe HR and BP response

↓

At 30 minutes of commencing dexmedetomidine infusion → reduce propofol infusion by 2ml

↓

Titrate both dexmedetomidine and propofol infusions at the same time as per guidance below

↓

**Dexmedetomidine titration**

Continue to **increase dexmedetomidine** infusion step-wise every 15 minutes to target RASS -1 to +1

Titrate any vasopressors as needed

Note: patient response varies individually and in some patients it may not be necessary to achieve the maximum infusion rate

**Propofol titration**

Continue to **reduce the propofol** infusion by 2ml every 15 minutes to target RASS -1 to +1

Titrate any vasopressors as needed

Note: patient response varies individually but some patients may continue to need background infusion of low-dose propofol

↓

**Combined effect of dexmedetomidine and propofol may cause bradycardia**

↓

**Treatment of bradycardia i.e. HR < 45**

1. Do not stop dexmedetomidine infusion
2. Reduce dexmedetomidine infusion by 2ml
3. Administer glycopyrolate as per protocol
4. Check that propofol infusion has also been reduced
5. Assess effect of all of the above
6. Inform medical staff if bradycardia persists

↓

**Stopping dexmedetomine**

- Dexmedetomidine should **not** be abruptly discontinued as rebound hypertension and/or agitation may occur
- Dexmedetomine does **not** need to be stopped for sedation interruption
- Following extubation the infusion rate can be gradually reduced e.g. step-wise every 15 mins

**Complete table below as infusion rates are titrated. Closely monitor the patient's BP and HR and observe the patient for signs of increasing wakefulness → target RASS -1 to +1**

| HR before commencing infusion _____ BP/MAP _____ | Time | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dexmedetomidine infusion rates for kg BW | | | | | | | | | | | | |
| Increase dexmedetmodine infusion every 15mins & tick √ box when infusion rate achieved | | | | | | | | | | | | |
| Start reducing propofol by 2ml at 30mins, then reduce by 2ml every 15mins & tick box √ to confirm | | | | | | | | | | | | |

## Adverse reactions

| Disorder | Common | Uncommon |
|---|---|---|
| **Metabolism & nutrition** | Hyperglycaemia<br>Hypoglycaemia | Metabolic acidosis<br>Hypoalbuminaemia |
| **Psychiatric** | Agitation | Hallucination |
| **Cardiac** | Bradycardia is very common<br>Myocardial ischaemia or infarction<br>Tachycardia | AV block first degree<br>Cardiac output decreased |
| **Vascular** | Hypotension **and** Hypertension is very common | |
| **Respiratory** | Respiratory depression | Dyspnoea<br>Apnoea |
| **Gastrointestinal** | Nausea, vomiting, dry mouth | Abdominal distension |
| **General** | Withdrawal syndrome<br>Hyperthermia | Drug ineffective<br>Thirst |

## Special warnings and precautions for use

## Advice relating to cardiac effects

- Heart rate and blood pressure is reduced and at higher concentrations peripheral vasoconstriction occurs. All patients should have continuous cardiac monitoring
- Hypotension does not normally require specific treatment, but where needed, users should be ready to intervene with dose reduction, fluids and/or vasoconstrictors
- Transient hypertension may be observed: decreasing the infusion rate may be advisable
- Signs of myocardial ischaemia or cerebral ischaemia: **dose reduction** should be considered
- Patients with pre-existing bradycardia: caution should be exercised. Bradycardia does not normally require treatment, but has commonly responded to anti-cholinergic medication or dose reduction
- Patients with impaired peripheral autonomic activity e.g. due to spinal cord injury, may have more pronounced haemodynamic changes after starting infusion and should be treated with care
- Alpha agonists have **rarely been associated with withdrawal reactions** when stopped abruptly after prolonged use. This possibility should be considered if the patient develops agitation and hypertension shortly after discontinuation of the infusion. **Gradual reduction in infusion** may be advisable

## Advice relating to respiratory effects

Respiration should be **monitored in non-intubated patients** due to the risk of respiratory depression and in some cases apnoea

## Advice relating to renal and hepatic clearance

- Renal - no dose adjustment is needed
- Hepatic - dexmedetomidine is metabolised in the liver. It is 94% bound to plasma proteins and should be used in caution in patients with hepatic impairment. **A reduced dose may be considered**

## Advice relating to combined sedative therapies

- Care should be taken if combining dexmedetomidine with other substances with sedative or cardiovascular actions as additive effects may occur. Studies have confirmed enhanced effects with propofol, alfentanil and midazolam. **Consider reducing adjunctive agent e.g. propofol by half as dexmedetomidine is initiated and incremented**
- Dexmedetomidine normally **does not cause deep sedation** and patients may be easily roused. This alone should not be considered as lack of efficacy in the absence of other clinical signs and symptoms
- Dexmedetomidine is used as an alternative to propofol. Patients will continue to need opioid analgesia

## Potential therapeutic value in Covid-19 patients admitted to ICU

The underlying protective mechanisms of dexmedetomidine include increasing parasympathetic tone, dampening of the inflammatory response, prevention of cell death, and inhibition of oxidative stress. By increasing parasympathetic tone and decreasing sympathetic tone, dexmedetomidine appears to confer protective effects on T cells and natural killer cells. Furthermore, its cholinergic anti-inflammatory mechanisms might suppress excessive inflammatory responses doi: 10.1016/j.bja.2020.09.031