FRCA Podcast

Episode 18 - Dexmedetomidine

Mechanism of action

Alpha-2 receptor agonist. It is highly selective. There is virtually no alpha-1 effect. Activation of alpha-2 (class B) receptors in the peripheral vasculature can lead to transient hypertension and reflex bradycardia with bolus doses. Bradycardia with hypotension arise due to reduced sympathetic outflow.

	Dexmedetomidine	Clonidine
α_2:α_1 receptor selectivity	1600:1	200:1
alpha-2 agonism	Full	Partial

Location of alpha-2 receptors	Clinical effect
Locus coeruleus (pons)	Sedation, anxiolysis, hypnosis
Cerebral cortex and hippocampus	Modulation of arousal, attention and cognition
Nucleus tractus solitarius and medullary vasomotor centre	Reduced sympathetic outflow, hypotension and bradycardia
Dorsal horn of the spinal cord (substantia gelatinosa)	Analgesia (inhibition of nociceptive transmission)

Dexmedetomidine crosses the blood brain barrier freely (it is lipophilic) but 94% of it is protein bound, so it is only the free drug fraction that is able to cross. It is broken down in the liver into inactive metabolites. This means that there should be a dose reduction in the context of liver impairment but there is no need to reduce the dose in renal failure.

Clinical effects and applications

Sedation that resembles natural sleep. It does not cause respiratory depression, and patients can be roused with verbal or physical stimulation. This means that it can be used for sedation on intensive care, sedation for MRI and CT scans, premedication, and as a means of facilitating awake craniotomy where patients are woken midprocedure and asked to follow some simple instructions. It is also useful when co-administered with TIVA for operations that require the patient to be spontaneously breathing, such as rigid bronchoscopy.

Side effects and contraindications

Bradycardia and hypotension. These result from an inhibition of sympathetic outflow from the CNS, namely the pons. This is exaggerated in patients who are hypovolaemic or bradycardic to start with, i.e. shock, heart block, antihypertensive medication, antiarrhythmics.

Likewise elderly patients or patients with chronic diseases such as hypertension or diabetes will not be able to compensate as readily for changes in their cardiovascular system. These are all relative contraindications to the use of Dexmedetomidine. Children may also become bradycardic, a reduction in heart rate by up to a third of the baseline rate can be expected.

Route of administration and dose

	Dexmedetomidine	Clonidine
Oral	Bioavailability < 20% (first pass metabolism)	2-4 mcg/kg (premedication) Bioavailability 80%
Nasal	1- 2 mcg/kg via MAD Bioavailability 80%	Volumes required for nasal administration are too large to make it a practical option.
Buccal	1-2 mcg/kg Bioavailability 80%	2-4 mcg/kg Bioavailability 80%
Intravenous	Bolus 0.5-1 mcg/kg Infusion 0.5-1 mcg/kg/hr (200 mcg/50 ml = 4 mcg/ml)	Bolus 1-2 mcg/kg Infusion 0.5-2 mcg/kg/hr (2500 mcg/50 ml = 50 mcg/ml) *
Neuaxial	1 mcg/kg	1-2 mcg/kg

Note: * Clonidine is often made up as a more concentrated solution when compared to Dexmedetomidine. This relates to how it is used in clinical practice. Dexmedetomidine is run as a titratable sedative, whereas Clonidine is often run as a background infusion on critical care (where drug volumes are kept to a minimum). In this context, Clonidine may also be given via the enteral route at a dose of 1-5 mcg/kg tds.

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Pharmacodynamics (intravenous)

	Dexmedetomidine	Clonidine
Speed of onset	5 minutes (intranasal 30minutes)	5 minutes (oral 45 minutes)
Peak effect	15-30 minutes	15-30 minutes
Steady state (infusion)	60 minutes	120 minutes
Duration of action	60-120 minutes (context sensitive half-time)*	6-12 hours

Pharmacodynamics (nasal and oral)

Pharmacodynamics	Dexmedetomidine (nasal)	Clonidine (oral)
Speed of onset	30 minutes	30-60 minutes
Peak effect	30-60 minutes	60-90 minutes
Duration of action	120 minutes (+/- 50%)	6-12 hours

Pharmacokinetics

	Dexmedetomidine	Clonidine
Volume of distribution	1.5 L/kg	2 L/kg
Protein binding	95%	20%
Metabolism	Hepatic 100%	Hepatic 50%
Excretion	Renal (metabolites)	Renal 50% (unchanged)
Clearance	16 ml/min/kg	2-4 ml/min/kg
Half-life (alpha) distribution	6 min	20 min
Half-life (beta) elimination	2 hours	12 hours

Context sensitive half-time (comparison to FENTANYL)

Duration of infusion *	Context sensitive half-time (Dexmedetomidine)	Context sensitive half-time (Fentanyl - for comparison)
10 minutes	4-8 min	10-15 minutes
1 hour	20-30 min	20-30 min
2 hours	40-60 min	60-120 min
4 hours	60-90 min	200-300 min
8 hours	90-120 min	> 300 min

Pharmacokinetic properties	Dexmedetomidine	Fentanyl
Elimination half-life	2 hours	3-6 hours
Clearance	16 ml/min/kg	10 ml/min/kg
Volume of distribution	1.5 L/kg	4 L/kg
Lipid solubility	High	Very high
Accumulation in tissues	Relatively limited	Marked
Recovery	Predictable	Prolonged

Note: * the duration of action of Dexmedetomidine after stopping the infusion is roughly equal to half the duration of the infusion, i.e. an infusion of < 2 hours duration will have a duration of action of 60 minutes after discontinuation, whilst an infusion of 4 hours duration will have a duration of action of 120 minutes after discontinuation. Compared to Fentanyl (a drug known to accumulate with prolonged infusions) Dexmedetomidine has a moderate volume of distribution, is rapidly cleared by the liver, does not accumulate in peripheral tissues, and has a short elimination half-life.