Clinical Update: 
**Dexmedetomidine and its Use in Neuroanesthesia**

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**Learner Objectives**

- Describe the pharmacologic properties of dexmedetomidine
- Explain α₂-receptor physiology and its contribution to dexmedetomidine’s unique clinical effects
- List the clinical indications for use in the operative setting
- Discuss the unique properties of dexmedetomidine that allows its use in neurosurgery
- Detail current trends for use in anesthetic practice
- Explain limitations of and alternatives to dexmedetomidine use

**History**

- Precedex (DEX) approved by the FDA in 1999
- DEX is the d-enantiomer of medetomidine, a medication that has historically been used for sedation in analgesia for veterinary medicine
- Fastest-growing IV sedative in 2009 and 2010

**Indications**

- Initially approved for sedation of intubated and mechanically ventilated patients in the intensive care setting for up to 24 hours
- In 2008, DEX was approved for use in non-intubated patients requiring sedation prior to and/or during surgical and other procedures, allowing its use by anesthesia providers for awake intubations and for MAC sedation
- Hospira is also seeking supplemental New Drug Application for long term use in the intensive care setting

**Dosage**

- Initial bolus dose of 1.0 mcg/kg administered over 10 minutes
- The approved maintenance dosages are 0.2 to 0.7 mcg/kg/hr for ICU sedation and 0.2 to 1 mcg/kg/hr for procedural sedation

**Pharmacokinetics**

- Distribution: DEX has a rapid redistribution half life (6 mins) and quickly disperses; becomes highly protein bound (94%)
- Exerts sedative effects 15 mins after loading dose; peak effects in 25 mins
- Does not accumulate (in healthy patients) in the first 24 hours
- Metabolism: Extensively metabolized in the liver (glucuronidation and cytochrome-P450 metabolism); doses should be reduced in patients with hepatic failure; renal impairment does not significantly affect the pharmacokinetics of DEX
- Elimination: Inactive metabolites are renally (95%) excreted

**Following this presentation, the learner should be able to:**

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**α and β Receptor Review**

- **α1** Arteriole constriction in skin, mucous membranes, and viscera, causing an increase in peripheral resistance, dilated pupils, and contracted bladder
- **α2** Reduced sympathetic outflow resulting in peripheral vasodilation
- **β1** Elevated chronotropy, dromotropy and intropy (HR, speed of conduction and force of contraction)
- **β2** Bronchodilation, dilation of arterioles in skeletal muscles resulting in decreased peripheral resistance, increased glycogenolysis and gluconeogenesis in the liver and bladder, relaxation resulting in decreased urine output

**Actually, there are 9**

- α1a, α1b, α1d
- β1, β2, β3
- α2a, α2b, α2c

**Nine Adrenoreceptors**

- Central vs peripheral
- Presynaptic vs postsynaptic
- Extrasynaptic
- DEX acts primarily at the α2a receptor

**α2 Selectivity**

- Norepinephrine
- Epinephrine
- Dopamine
- Clonidine
- Guanabenz
- Medetomidine
- Dexmedetomidine

**Selectivity:**
- Clonidine: α1, 250:1
- DEX: α1, 1,620:1

**α2 Receptor Subtypes**

- **α2A** Locus ceruleus
  - Vagomimetic action
  - Blocks T1-T4 (cardioaccelerator fibers)
- **α2B** Thermoregulatory inhibition in CNS
- **α2C** Brainstem vasomotor center
  - Anxiolysis
  - Cerebral vessels and peripheral vasculature
- **α2D** Peripheral smooth-muscle cells
- **α2E** Dorsal horn of spinal cord

**Density of α2 Receptors**

- While awake, the locus ceruleus provides NE-mediated inhibition of the ventrolateral preoptic nucleus in the hypothalamus.
- Adenosine, one of the brain’s principal somnogens, accumulates from degradation of ATP during periods of prolonged wakefulness. Binding of adenosine in the ventrolateral preoptic nucleus is associated with increased activity (and therefore increased sleep).
- Adenosine binding and inhibition of the locus ceruleus lead to activation of the ventrolateral preoptic nucleus, which inhibits the ascending arousal circuits and promotes non-REM sleep.

**Physiology of Sleep**

- While awake, the locus ceruleus provides NE-mediated inhibition of the ventrolateral preoptic nucleus in the hypothalamus.
**Physiology of Sleep**

**DEX-Induced Sleep:**
- DEX hyperpolarizes the locus ceruleus, inhibiting the release of norepinephrine
- Decreased firing by locus ceruleus allows the ventrolateral preoptic nucleus to reduce arousal by inhibiting the ascending noradrenergic pathway
- Summary: The EEG patterns of DEX-induced sedation closely resemble those of non-REM sleep

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**Clinical Effects of DEX**

Agonism of α₂ receptor causes:
- Dose dependent sedation and anxiolysis
- Analgesia (supraspinal & spinal sites)
- Decreased plasma catecholamines
- Centrally-mediated bradycardia and hypotension
- Diuresis due to inhibition of ADH release and antagonism of ADH tubular effects
- Decongestant and antisialogogue effects

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**CNS Effects**

Locus ceruleus
- Reduces neuronal firing, leading to sedative and hypnotic response
Medullary dorsal motor nucleus of the vagus
- Bradycardic and hypotensive effects
Intermediolateral cell column and substantia gelatinosa of the spinal cord
- Inhibits release of the nociceptive mediator substance P and mediates the analgesic effect
Cerebral vasculature
- Cerebral vasoconstrictor
- Decreases cerebral blood flow

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**Respiratory Effects**

Does not significantly alter:
- pH
- PaO₂
- PaCO₂
- Respiratory Rate
- Oxygen Saturation

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**Adverse Effects**

The MOST COMMON adverse events with DEX are

**Hypotension and Bradycardia**

which can be treated with standard medical intervention such as IV fluids, positioning, or administration of vasopressors such as epi, atropine or glycopyrrolate

*Proceed with caution with elderly, hyponolemia and chronic hypertensives
Cardiovascular Effects

Increasing Concentrations
- ↑ Sedation
- ↑ Analgesia
- ↓ Heart rate
- ↓ Cardiac output
- ↓ Memory

Biphasic response (low, then high)
- Mean arterial pressure
- Pulmonary artery pressure
- Vascular resistance

Safety

Reported overdoses
- 3 Adult patients
  - 2.6x dose for 20 minutes preoperatively for skin grafting
    - BIS 22-30
  - 10x dose post CABG for over 7 hours
    - Unarousable
  - 60x dose for 15 minutes post debridement
    - Unarousable
- All patients maintained hemodynamic stability
- After discontinuation of infusion all patients returned to baseline
- Unremarkable recoveries

Pediatric overdose
- 21 mo for MRI of brain
- Ordered bolus 2 mcg/kg over 10 minutes
- Ordered infusion 1 mcg/kg/hr
- Actual infusion 1 mcg/kg/min
  - 60 x intended dose
- 20 minutes to reach Aldrete score 9
- 2 hours to reach baseline neuro status
- Vital signs stable during procedure and recovery period
- Kept overnight for observation
- Uneventful stay

DEX and Volatile Agents

Patients for supratentorial craniotomy
- Desflurane, Sevoflurane, and Isoflurane
  - No patient required administration of vasodilator
  - No patient required administration of vaspressor
  - Similar wake up times
  - Desflurane had significantly shorter:
    - Time to eye opening following verbal command
    - Time to orientation

Intubation and Extubation

Fiber optic intubation
- Calmer and more cooperative with FOI than with midazolam alone
- Greater patient satisfaction
- No hemodynamic differences

Extubation after intracranial surgery
- 0.5 µg/kg IV over 60 seconds 5 minutes prior to completion of surgery
- Decreased MAP
- No difference in recovery time
- Extubated without coughing
**Neuroanesthesia Wish List**

Desire a drug that can offer:
- Ease of control (e.g., rapid onset/offset)
- Intracranial homeostasis
- Intraoperative hemodynamic stability
- Noninterference with neurophysiologic monitoring
- Neuroprotection
- Antinociception

**Uses in Neuroanesthesia**

- Awake craniotomy
- Traditional craniotomy
- Carotid endartarectomy
- Deep brain stimulator
- Spinal surgery
- Aortic aneurysm repair

**Options for Neuroanesthesia**

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**Addition of DEX to TIVA regimen:**
- No clinically significant effect on SSEP monitoring
  - Within 50% baseline amplitude
  - Within 10% baseline latency
- No clinically significant effect on MEP monitoring
- Decreased Propofol requirements
- Decreased narcotic requirements

**Neurophysiological Monitoring**

**Effect of DEX on SSEPs**

**Asleep-Awake-Asleep**

- Motor and language mapping
- Deep brain stimulator placement

**Role of DEX**

- Maintains respirations
- Allows for cooperative sedation
- Hemodynamic stability
- Safe in pediatric population

**Awake Craniotomy**
Language testing performed during an awake craniotomy in a patient sedated with DEX

**Video Clip: Speech Mapping**

http://www.youtube.com/watch?v=AFXjOEpV22s

**Neurovascular injury**

- Aneurysm clipping
- Excision of AVM
- Parenchymal brain tissue $\text{PO}_2$ ($PbrO_2$) monitoring
  - No significant reduction of $PbrO_2$
  - Modest increase in $PbrO_2$ with modest increase in MAP
- Did not cause reduce cerebral blood flow to injured area with already compromised oxygenation

**DEX in neurovascular surgery patients:**

- Aneurysm clipping
- Excision of AVM
- Parenchymal brain tissue $\text{PO}_2$ ($PbrO_2$) monitoring
  - No significant reduction of $PbrO_2$
  - Modest increase in $PbrO_2$ with modest increase in MAP
- Did not cause reduce cerebral blood flow to injured area with already compromised oxygenation

**Neuroprotection**

DEX improved neuronal survival after transient global or focal ischemia in rats.

Several theories of mechanism:

- Balance between apoptotic and antiapoptotic proteins
- Reduced glutamate release
- Enhanced glutamine disposal by oxidative metabolism in astrocytes

**Neuroprotection**

DEX after pituitary surgery did not have an effect on lumbar CSF pressure.

**Neurostabilization**

DEX in the presence of volatile anesthetics decreased CBF but oxygen consumption was maintained. There was no evidence of cerebral ischemia in this dog model.

**Neurostabilization**

DEX had no detrimental effect on local brain tissue oxygenation, suggesting maintenance of the cerebral oxygen supply-to-demand relationship.

**Interview: DEX in Awake Craniotomies**

Dr. Steven Toms, Director of Neurosurgery, Geisinger Medical Center, Danville, PA, describes how Dexmedetomidine facilitates an awake craniotomy.
**Case Report 1**

**Planned Procedure:** Posterior thoracolumbar fusion with SSEP & MEP monitoring

**Patient:** 15-year-old female  
Ht: 1.625m  
Wt: 48 kgs  
Allergies: None known

**Relevant Medical History:** Idiopathic scoliosis, hypoplastic right lung disease, asthma, scarlet fever, and pneumonia

**Current Medications:** Daily MVI and Albuterol inhaler, used occasionally

**Preop Assessment:** Lungs clear to auscultation, regular heart rate & rhythm

**Airway Assessment:** Mallampati 2, thyromental distance 3 fingerbreadths

**Preop Education:** Prior to induction, the surgeon and the anesthesia team discussed the intraop wake-up test with the patient

**Induction:** Standard inhalational mask induction with Sevo, N₂O and O₂  
After IV x 2 placed, pt given:  
- Fentanyl 250 mcg  
- Lorazepam 1 mg  
- Rocuronium 30 mg

Direct laryngoscopy performed and atraumatic intubation with 7-mm ETT, +ETCO₂ & equal bilateral breath sounds noted

**TIVA** started following induction:  
- DEX 0.9 mcg/kg/hr  
- Ketamine 0.4 mg/kg/hr  
- Fentanyl 1 mcg/kg/hr

**Neurologic monitoring** placed and pt positioned prone with meticulous attention to proper positioning and padding of pressure points

**Maintenance Anesthesia:**  
- N₂O 60% + O₂ 40%  
- DEX 0.9-1.2 mcg/kg/hr  
- Ketamine 0.4-0.6 mg/kg/hr  
- Fentanyl 1-2 mcg/kg/hr  
- Pt recovered from induction dose of muscle relaxant with TOF 4/4

**Prior to wake up test:**  
- Fentanyl was turned off 30 minutes prior  
- DEX & Ketamine turned off 5-10 minutes prior  
- Pt awakened promptly, squeezed hands and moved feet on command as discussed preoperatively

Anesthesia resumed following testing with Propofol 50 mg bolus and Lorazepam 1 mg. DEX, Ketamine and Fentanyl infusions were resumed at previous rates.

**Additional Intraoperative Information:**  
- Total surgical time was 9 hours  
- EBL 1,100 mL  
- Pt received 1,000 mL IV Hetastarch, 3,150 mL LR; 1 U autologous prbcs; and 502 mL autologous prbcs from Cell Saver  
- Total of 250 mcg of Phenylephrine was administered in 50 mcg increments for BP support  
- Results of SSEPs & MEPs remained satisfactory throughout the case

**Postop:**  
- Pt spontaneously breathing, opened eyes & followed commands. Extubated in OR and admitted to PICU.  
- When interviewed, pt had no recollection of intraop wake-up test  
- Pt did not require pain medication until 10 hrs postop  
- Discharged to home 6 days postop

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**Case Report 2**

**Planned Procedure:** Left front awake craniotomy for resection of glioma

**Patient:** 66 year-old male  
Ht: 1.855 m  
Wt: 116 kgs  
Allergies: Sulfa, Oxycontin

**Relevant Medical History:** Complex partial seizures with suspected frontal lobe glioblastoma, TIA’s, Depression, Sustained closed head injury from MVA in 1966

**Premedication:** Midazolam 2 mg

**Induction:** Placed on 4L oxygen via nasal cannula and given DEX bolus of 1 mcg/kg over 20 mins. Prior to placement of Mayfield pins, localization of scalp per surgeon with mixture of Bupivacaine 0.5% + Lidocaine 1% + Epi 1:200,000 solution. Propofol bolus of 50 mg by CRNA.

**Maintenance:**  
- Primary: DEX infusion of 0.4 – 0.6 mcg/kg/hr  
- Adjuncts: Intermittent boluses of Propofol 20-40 mg during periods of stimulation in addition to one-time doses of Ketamine 15 mg, Midazolam 2 mg (for total of 4 mg), and Fentanyl 25 mcg.

**Neurologic monitoring** performed after bone flap excised and dura opened per surgeon. Pt allowed to fully awaken and speech and motor testing performed successfully.
For patient wake up testing:
- DEX infusion decreased from 0.6 to 0.4 mcg/kg/hr.
- Pt awakened and was able to squeeze hands, move feet and verbally respond on command as discussed preoperatively.

Intraoperative:
Approximately 4 hours into the case and during completion of the resection, the patient became very agitated and jerked his head out of the Mayfield pins. The patient grabbed the drapes and began trying to move off of the OR table.

The decision was made to move more deeply sedate the patient to maintain safety. The pt was given a Propofol bolus of 100 mg and an LMA #3 was inserted. Maintenance anesthesia was adjusted accordingly:
- DEX 0.4 mcg/kg/hr
- Propofol 25 mcg/kg/min
- Phencyclidine 50 mcg/min

Case Report 2

DEX and Ketamine – potential for balanced anesthetic

Patient selection – importance of preanesthetic evaluation

Timing of bolus dosing

Case Discussion

Additional Intraoperative Information:
- Total surgical time was 8 hours
- EBL: 200 mL
- Pt received 2,600 mL IV Plasma electrolyte: UOP was 1,175 mL
- Mannitol 50 grams and Dexamethasone 10 mg were given as requested by surgeon for visualization soon after induction. In addition, Zofran 4 mg was given for prophylactic PONV treatment.
- Results of SSEPs remained satisfactory throughout the case; direct cortical stimulation failed to reveal motor response. Stereotactics were lost after patient agitation and self removal of Mayfield pins.

Postop:
- At the end of surgery, pt spontaneously breathing, opened eyes & followed commands. LMA removed in OR and taken to PACU.
- In PACU, pt found to be aphasic and had a R hemiplegia
- CT & MRI did not immediately show signs of ICH or stroke
- Discharged to rehabilitation facility 3 days postop and then to home

Summary

DEX has various niche indications for use as an anesthesia adjunct or primary agent
- Patient selection important – personality and health status
- Patient preparation extremely important if wake up testing used
- Look for R&D on products that are α₂ subtype specific

References


References