# P R _ _ _ _ _ _

## An overview of Precedex (Dexmedetomidine)

By: Andy Baum, CRNA

# Disclosures

- I have no relationships to disclose

# Goals:

- Pharmacology of Dexmedetomidine (Precedex)
- Dexmedetomidine (Precedex) in anesthesia
- Dosing and clinical applications of Dexmedetomidine (Precedex)

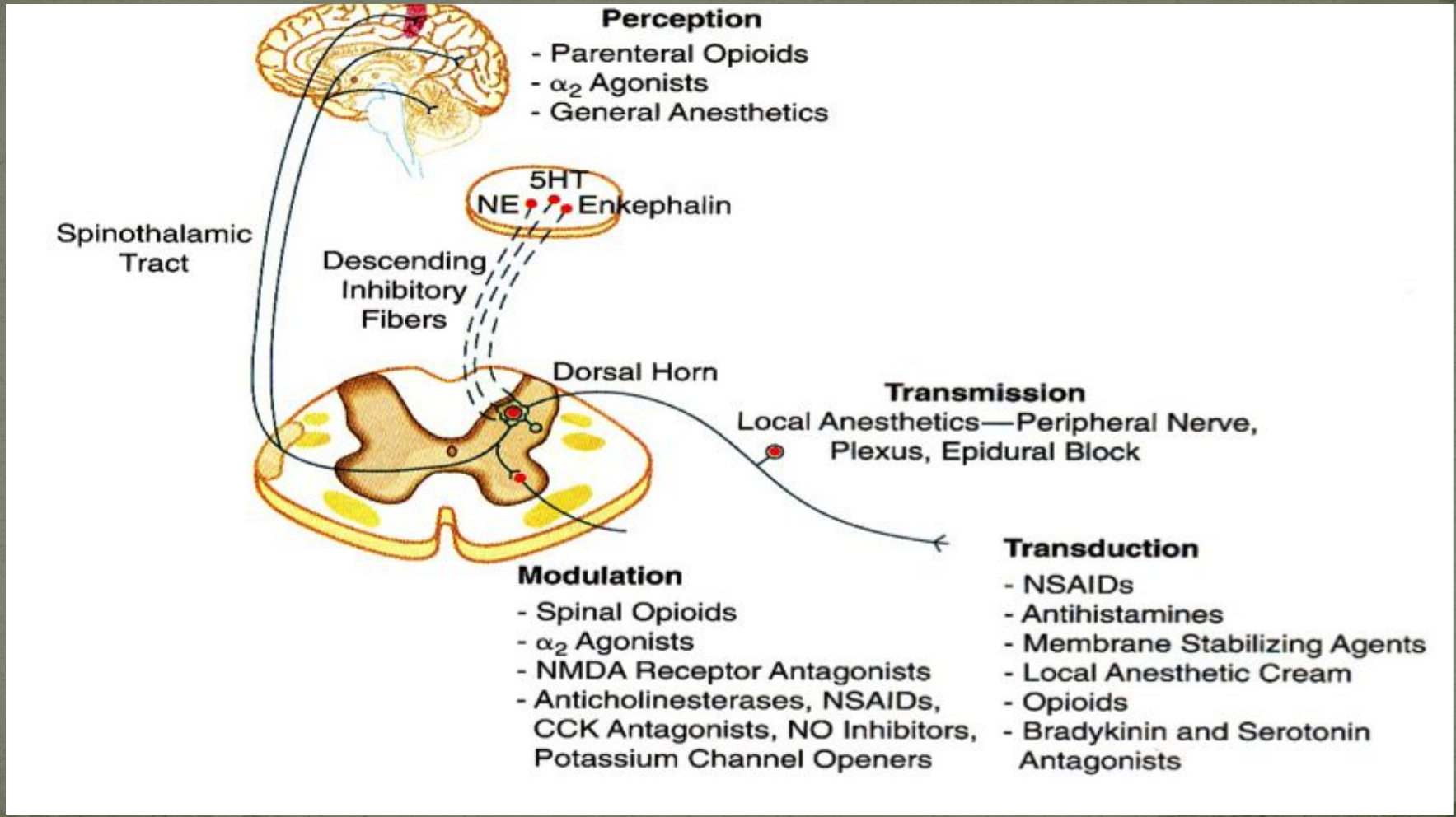
# Refresher on Pain

- Transmission-
  - Conduction of electrical impulses to CNS (through 1st, 2nd , and 3rd order neurons). The major connections for these nerves located in the dorsal horn of SC and thalamus with projections into the somatosensory cortices

  - Basically how and action potential travels from periphery to CNS
- Transduction-
  - Process by which a noxious stimulus (i.e. thermal, chemical, or mechanical stimuli) is converted to an electrical impulse (action potential) in the sensory nerve endings
- **Modulation**-
  - Process of altering **afferent** pain transmission along the pain pathway. Both inhibitory and excitatory mechanisms modulate pain impulse transmission in the CNS and PNS (Modulation can be either inhibitory or augment the nerve impulses)
- **Perception-**
  - Occurs in the thalamus, where the cortex discriminates specific sensory experiences. Occurs once the stimulus of the pain is recognized by various areas in the brain, primarily within the cortex (somatosensory area).

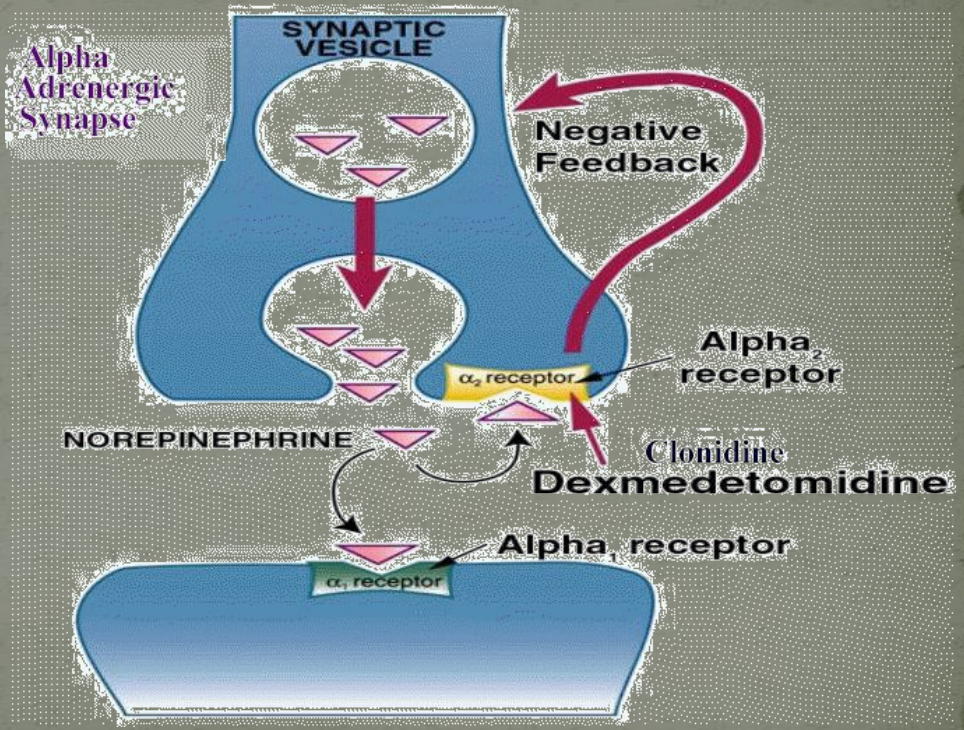
| Drugs | Targets | Mechanisms | Functional Consequences | Side Effects |
|---|---|---|---|---|
| Opioids | G protein–coupled μ-, δ-, κ-receptors | ↓ cAMP<br>↓ $Ca^{2+}$ currents<br>↑ $K^+$ currents | ↓ Excitability of peripheral and central neurons<br>↓ Release of excitatory neurotransmitters | μ, δ: sedation, nausea, euphoria/reward, respiratory depression, constipation<br>κ: dysphoria/aversion, diuresis, sedation |
| NSAIDs | Cyclooxygenases (COX-1, COX-2) | ↓ Prostaglandins<br>↓ Thromboxanes | ↓ Sensitization of sensory neurons<br>↑ Inhibition of spinal neurons | Nonselective: gastrointestinal ulcers, perforation, bleeding, renal impairment<br>COX-2: thrombosis, myocardial infarction, stroke |
| Serotonin agonists | G protein–coupled 5-HT receptors<br>$5\text{-HT}_3$: ion channels | ↓ cAMP ($5\text{-HT}_1$)<br>↑ cAMP ($5\text{-HT}_{4\text{-}7}$)<br>↑ PLC ($5\text{-HT}_2$) | ↓ Release of excitatory neuropeptides<br>↓ Neurogenic inflammation<br>↑ Vasoconstriction | Myocardial infarction, stroke, peripheral vascular occlusion |
| Antiepileptics | $Na^+$, $Ca^{2+}$ channels<br>GABA receptors | ↓ $Na^+$ currents<br>↓ $Ca^{2+}$ currents<br>↑ GABA receptor activity | ↓ Excitability of peripheral and central neurons<br>↓ Release of excitatory neurotransmitters | Sedation, dizziness, cognitive impairment, ataxia, hepatotoxicity, thrombocytopenia |
| Antidepressants | Norepinephrine/5-HT transporters<br>$Na^+$, $K^+$ channels | ↓ Norepinephrine/5-HT reuptake<br>↓ $Na^+$ currents<br>↑ $K^+$ currents | ↓ Excitability of peripheral and central neurons | Cardiac arrhythmia, myocardial infarction, sedation, nausea, dry mouth, constipation, dizziness, sleep disturbance, blurred vision |

cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine; NSAIDs, nonsteroidal anti-inflammatory drugs; PLC, phospholipase C.


Perception
- Parenteral Opioids
- $\alpha_2$ Agonists
- General Anesthetics
5HT
NE
Enkephalin
Spinothalamic Tract
Descending Inhibitory Fibers
Dorsal Horn
Transmission
Local Anesthetics—Peripheral Nerve, Plexus, Epidural Block
Modulation
- Spinal Opioids
- $\alpha_2$ Agonists
- NMDA Receptor Antagonists
- Anticholinesterases, NSAIDs, CCK Antagonists, NO Inhibitors, Potassium Channel Openers
Transduction
- NSAIDs
- Antihistamines
- Membrane Stabilizing Agents
- Local Anesthetic Cream
- Opioids
- Bradykinin and Serotonin Antagonists

# Alpha 2-Adrenergic Agonists

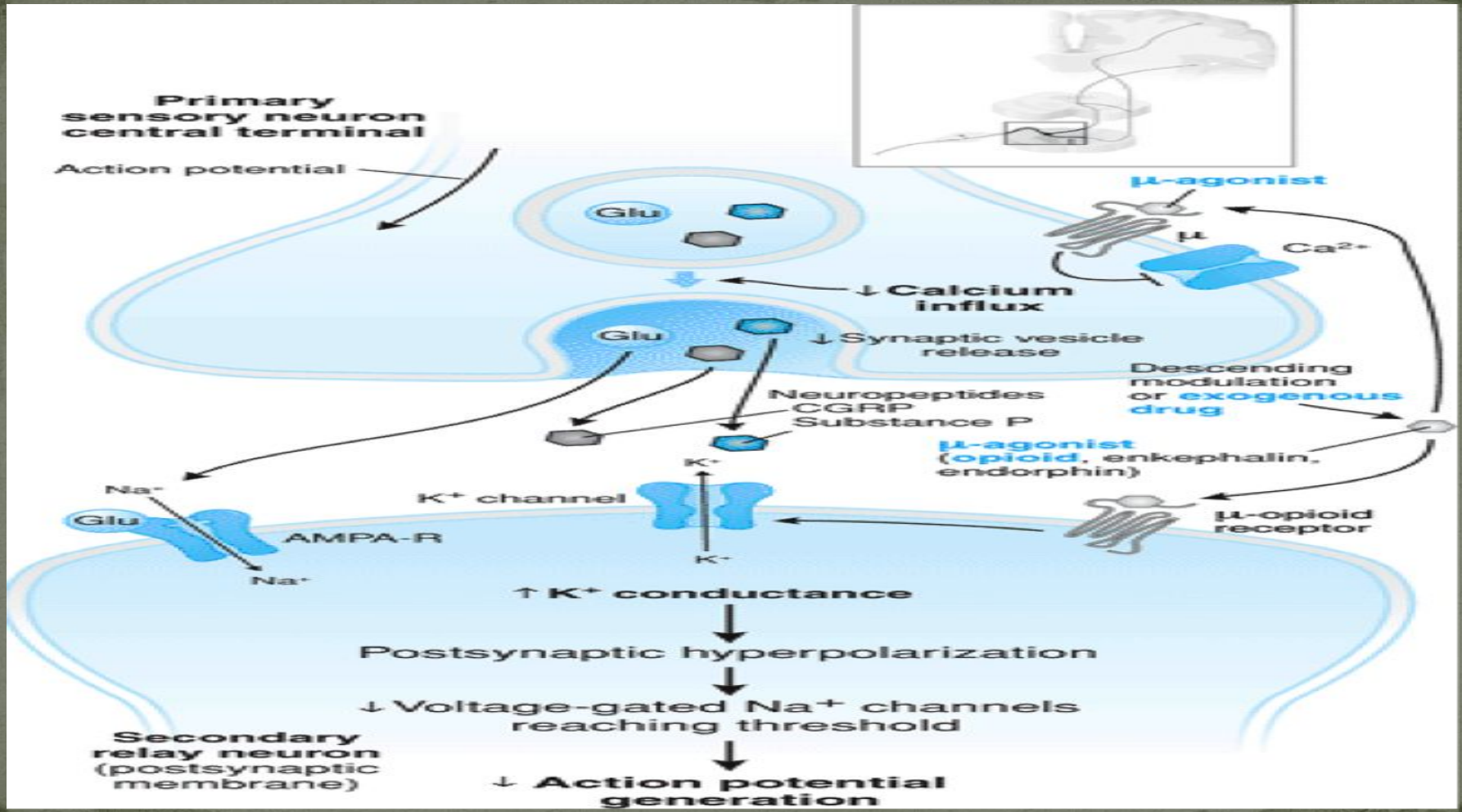
- Exhibit analgesic and anxiolytic effects by:
  - **activating postsynaptic K+ channels (increase K+ efflux)**
  - Inhibiting presynaptic Ca++ channels (decrease Ca++ influx)
  - Binds with pre/ post synaptic A2 receptors in CNS increase NE levels sedation and analgesia by increasing inhibitory NTs

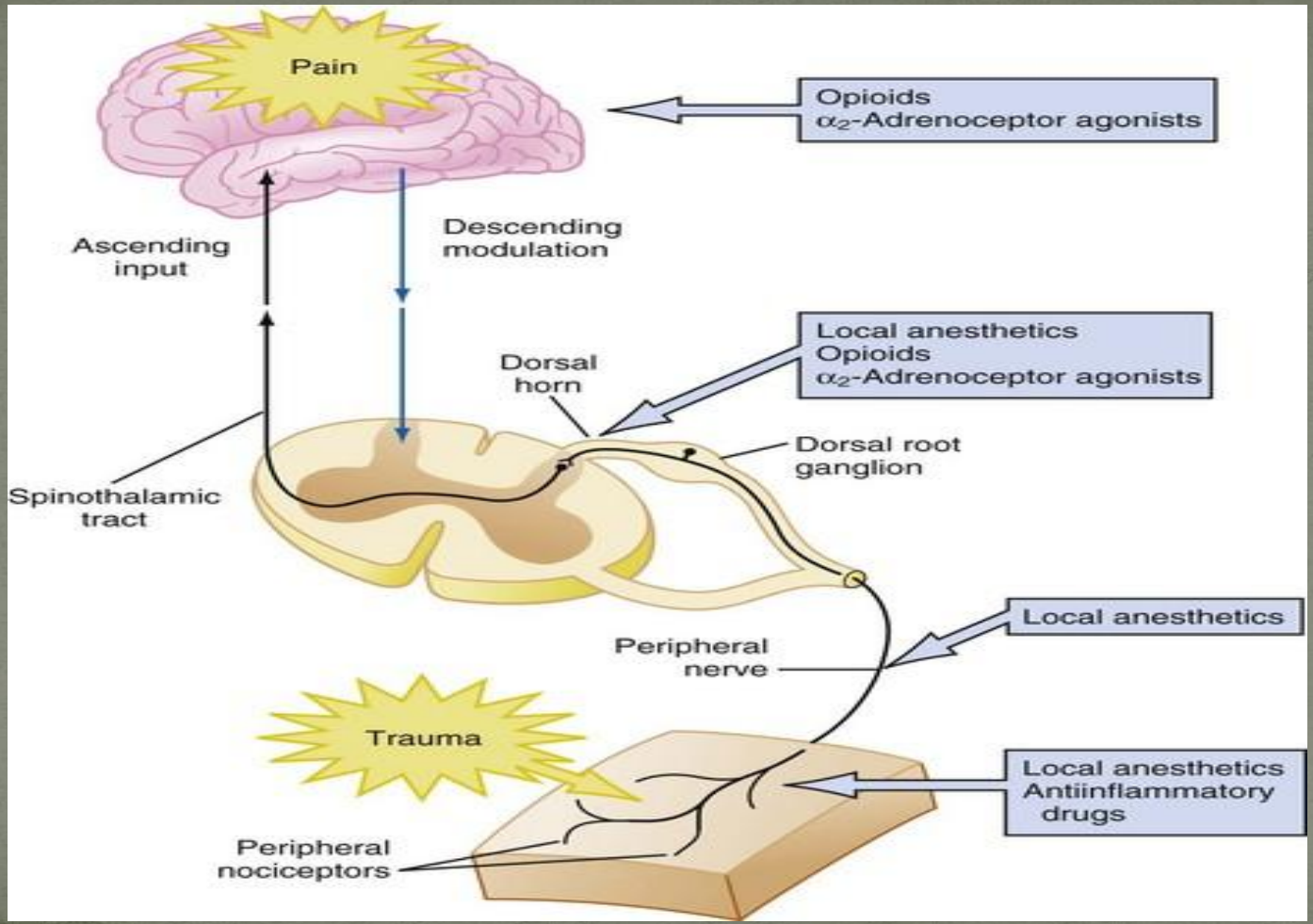


# Neurotransmitters

| Neurotransmitter | Receptor[1] | Effect on Nociception |
|---|---|---|
| Substance P | NK–1 | Excitatory |
| Calcitonin gene-related peptide | | Excitatory |
| Glutamate | NMDA, AMPA, kainite, quisqualate | Excitatory |
| Aspartate | NMDA, AMPA, kainite, quisqualate | Excitatory |
| Adenosine triphosphate (ATP) | $P_1$, $P_2$ | Excitatory |
| Somatostatin | | Inhibitory |
| Acetylcholine | Muscarinic | Inhibitory |
| Enkephalins | $\mu$, $\delta$, $\kappa$ | Inhibitory |
| $\beta$-Endorphin | $\mu$, $\delta$, $\kappa$ | Inhibitory |
| Norepinephrine | $\alpha_2$ | Inhibitory |
| Adenosine | $A_1$ | Inhibitory |
| Serotonin | 5-$HT_1$ (5-$HT_3$) | Inhibitory |
| $\gamma$-Aminobutyric acid (GABA) | A, B | Inhibitory |
| Glycine | | Inhibitory |

**Excitatory NTs- mediate pain** **Inhibitory NTs- inhibit pain**


Primary sensory neuron central terminal
Action potential
Glu
μ-agonist
μ
Ca2+
↓Calcium influx
Glu
↓Synaptic vesicle release
Descending modulation or exogenous drug
Neuropeptides
CGRP
Substance P
μ-agonist (opioid, enkephalin, endorphin)
K+
Na+
K+ channel
Glu
AMPA-R
μ-opioid receptor
Na+
K+
↑K+ conductance
Postsynaptic hyperpolarization
↓Voltage-gated Na+ channels reaching threshold
Secondary relay neuron (postsynaptic membrane)
↓Action potential generation


Pain
Opioids
α2-Adrenoceptor agonists
Ascending input
Descending modulation
Local anesthetics
Opioids
α2-Adrenoceptor agonists
Dorsal horn
Dorsal root ganglion
Spinothalamic tract
Local anesthetics
Peripheral nerve
Trauma
Local anesthetics
Antiinflammatory drugs
Peripheral nociceptors

# Dexmedetomidine (Precedex) Dosing

- A highly selective A2 adrenergic agonist
- Rapid onset of action (5 minutes)
- Short duration of action (about 2-4 hours, but dose dependent)
- Anxiolytic, ANALGESIC, sedative and hypnotic properties
- SIDE EFFECTS: Sedation, bradycardia, HYPOtension
  - LITTLE- NO RESPIRATORY DEPRESSION!!

# Dexmedetomidine (Precedex) Dosing

- IV Analgesic doses:
  - Bolus: 0.5- 1 mcg/kg over 10-20 min * recommended to start preop
  - Infusion: 0.4- 0.8 mcg/kg/hour

# Dexmedetomidine (Precedex) Dosing

- Regional Anesthesia doses:
  - Neuraxial
    - Epidural: 25- 50 mcg
      - Alternatives: Clonidine (1 mcg/kg; 50-100 mcg)
    - Spinal: 5-10 mcg
      - Will prolong duration of nerve block
  - Peripheral Nerve Blocks
    - 25-50 mcg; may prolong PNB by 20-25%

# Who? What? When? Where? Why?

- Procedural Sedation
  - Endoscopies, Awake FO, Radiology, etc
- Moderate Anesthesia
- General Anesthesia
- Regional Anesthesia

An all inclusive drug:

- Anxiolytic, ANALGESIC, sedative and hypnotic propertie
- Reduction on PONV, postoperative shivering

# Discussion/ Questions