Opioids

Clinical uses:
- Analgesia
- Decrease MAC
- Smooth anesthetic
- Antitussive

Disadvantages:
- Respiratory Depression
- Nausea/Vomiting
- Bradycardia
- Hypotension
- Urinary retention
- Dysphoria/Euphoria
- Prolonged emergence
- Truncheal rigidity

As a single agent, opioids yield inferior sedation!

Fentanyl

- Potency: 75-125x more potent than morphine as an analgesic
  - More rapid onset and shorter duration
- Speed of onset: 3.5-6 minutes
- Duration: 30-60 minutes
- Low dose (1-2ug/kg) causes analgesia
- Higher doses (2-20ug/kg) blunt responses to intubation/surgery
- Recurrent respiratory depression
Remifentanil
- Ultra short acting opioid - mu agonist
- Ester linkage renders it susceptible to hydrolysis by plasma and tissue esterases
- **Rapid speed of onset:** 1-2 minutes
- **Context sensitive T\(_{1/2}\):** 3-10 minutes – regardless of duration
- Intense levels of analgesia of short duration
- No residual opioid effects
- More rapid recovery

Remifentanil Complications
**Common**
- Bradypnea (<8 bpm) – minutes
- Nausea / Vomiting
- Pruritis
**Rare**
- Hypotension
- Bradycardia
- Chest Wall Rigidity

Remifentanil
- Often used in a Propofol admixture
- 100mcg remifentanil + 200mg Propofol
- Used in a continuous infusion pump
  - Loading bolus or micro boluses of 150mcg/kg/min
  - Initial infusion 70mcg/kg/min
- Works to counter effect the lack of propofol analgesic effects
- Utilizes significantly less Propofol
**OPIOIDS**

**Patient Management**
1. Acute intoxication
2. Chronic administration due to recognized medical indication
3. Use of long-acting opioid antagonists
4. Use of long-acting opioid antagonists & agonist/antagonist combinations

**1. Management – Acute Intoxication**

**2. Chronic Medical Administration**

Patient likely not forthcoming
Must respect patient tolerance
*Awareness of synergistic effects with other anesthetic agents – benzodiazepines
Preparation to immediately provide airway management
*Avoid antagonists and agonist/antagonists
*Anesthetic administration – ‘Start Low & Go Slow’

**3. Use of long-acting opioid antagonists**

Naltrexone – T1/2 – 4-10 hours
Reduces euphoria, craving, withdrawal
Methadone – T1/2 – 24+ hours
Also inhibits serotonin reuptake
Also inhibits norepinephrine reuptake
Also antagonizes NMDA receptors
Eg. Ketamine, Nitrous Oxide, Tramadol
Physical dependence persists
OPIOIDS
Management of the Medically Dependent
4. Use of long-acting opioid antagonists & agonist/antagonist combinations

AT-121
EXPERIMENTAL ANALGESIC
ACTS AT OPIOID MU AND NOCICEPTION RECEPTORS
100X BETTER AT REDUCING PAIN IN MONKEYS THAN MORPHINE
NOCICEPTION RECEPTORS COUNTERACT THE EXPERIENCE OF PLEASURE
ABUSE & DEPENDENCE RELATED EFFECTS BLOCKED
NO RESPIRATORY DEPRESSION
2-3 YEARS – DOSE RESPONSE & CLINICAL STUDIES

Ketamine
Phencyclidine derivative producing 'dissociative' anesthesia
- Dissociation between thalamus and limbic system
Cataleptic state
- Eyes open
- Slow nystagmic gaze
- Noncommunicative
- Amnesia present
- Dose dependent analgesia
**Ketamine**

**Mechanisms of Action...**
- Antagonist NMDA Receptor
- Agonist Adrenergic Receptors
- Antagonist Muscarinic Receptors CNS
- Blocks Reuptake of Catecholamines
- Agonist at opioid Sigma Receptor

**Water Soluble, Permits Administration...**
- IV, IM, Intranasal, Oral, Rectal

---

**Ketamine**

**Respiratory Effects**
- Intact Reflexes
- Maintenance FRC
- Response to Hypercarbia Maintained
- Bronchodilator

**Cardiovascular Effects**
- Increased HR
- Increased BP
- Increased CO
- Direct Myocardial Depressant

---

**Ketamine – Modifying Adverse Effects**

**Emergence Phenomenon**
- Reducing Incidence --
  - Benzodiazepines
  - Environmental Factors
- Potentiating Incidence --
  - Atropine / Scopolamine
  - Droperidol

**Hypersalivation**
- Reducing Incidence – Glycopyrrolate

**Analgesia**
- IV 0.3mg/kg = 0.1mg/kg morphine
  - Partial reversal by Naloxone

---

---
**Propofol**

1% Isopropyl Phenol

Very Lipophilic

Delivery in oil-in-water emulsion

- 10% Soybean Oil
- 2.25% Glycerol
- 1.2% Egg Phosphatide - Lecithin not Albumin

**Not contraindicated in most egg allergies**

‘Yolk not the egg White’

*Overall the prevalence of allergy to propofol is 2.3% - not associated with egg allergy*

---

**Applications of Propofol**

- Hypnosis
- Sedation
- Amnesia
- Muscle Relaxation
- Antiemetic
- Mood Alteration
- Anticonvulsant

---

**Propofol**

**Clinical Effects**

- Hypotension (20-30% decrease BP)
- Exaggerated in Hypovolemia, Elderly
- No change in heart rate
- Dose dependent depression ventilation
- Rapid, smooth emergence

**Adverse Effects**

- Pain on Injection
- Hypotension
- Post-Sedation Neuroexcitation
- Sepsis
Drugs subject to hepatic metabolism or renal excretion are metabolized at 1/2 to 1/3 the rate of younger adults
- Fentanyl = 50% less for 85 yr old
- Midazolam = 30% less for 60yr old
  60% less for 80 yr old
- Diazepam = 66% less for the geriatric patient
- Propofol = 18% less for 65 yr old
- More pronounced hypotension

---

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Midazolam</th>
<th>Diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolites</td>
<td>Insignificant</td>
<td>Yes</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>1.5-2.6</td>
<td>20-80</td>
</tr>
<tr>
<td>Unique Effects</td>
<td>Greater amnesia &amp; BP decline</td>
<td>Vein irritation</td>
</tr>
<tr>
<td>Formulations</td>
<td>1mg and 5 mg/mL</td>
<td>5 mg/mL</td>
</tr>
<tr>
<td>IV Increment</td>
<td>1-2 mg</td>
<td>2.5-5 mg</td>
</tr>
<tr>
<td>Duration *</td>
<td>15-30</td>
<td>15-30</td>
</tr>
<tr>
<td>PO Doses</td>
<td>0.5-0.75mg/kg</td>
<td>10-20mg</td>
</tr>
</tbody>
</table>

* Estimates – patient may require additional doses more often

---

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Triazolam</th>
<th>Diazepam</th>
<th>Lorazepam</th>
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<tbody>
<tr>
<td>Metabolites</td>
<td>Insignificant</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>1.5-5.5</td>
<td>20-80</td>
<td>10-20</td>
</tr>
<tr>
<td>Onset PO (min)</td>
<td>30-45</td>
<td>60-90</td>
<td>90-120</td>
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<tr>
<td>Duration (hr)</td>
<td>1-2</td>
<td>2-4</td>
<td>3-6</td>
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<tr>
<td>Anxiolysis Dose (mg)</td>
<td>0.125-0.25</td>
<td>5-10</td>
<td>2-4</td>
</tr>
<tr>
<td>Sedation Dose (mg)</td>
<td>0.5-0.75</td>
<td>10-20</td>
<td>4-6</td>
</tr>
</tbody>
</table>
α₂-agonists

Medications act at the α₂ adrenergic receptor which exist in the central and peripheral nervous system resulting in...
- Sedation
- Analgesia
- Muscle Relaxation
- Stable respiratory rates
- Predictable cardiovascular responses

Selectivity of α₂-agonists

- Selective...

Clonidine - α₁:α₂ specificity 1:220
More vascular sympatholytic effect
Normotensive
Avoids tachycardia

- Highly Selective...

‘Dex’ - α₁:α₂ specificity 1:1620
Decrease sympathetic activity without paralysis of compensatory homeostatic reflexes

Oral Clonidine - Premedicant

Dosing (4mcg/kg)
- Adults: 0.2mg oral or sublingual
- Elderly: 0.1mg

Effects
- Sedation
- Does not cause amnesia
- Postoperative analgesia
- Reduces anesthetic requirements
- Reduces postoperative nausea/vomiting
Oral Clonidine - Premedicant

**Contraindications**
- Pre-Procedure Hypotension
- Autonomic Dysfunction
- Pre-Procedure Bradycardia
- Severe Coronary Artery Disease
- Cardiac Conduction Abnormalities
- Chronic Renal Failure
- Cerebrovascular Disease

Dexmedetomidine

- Utilized Oral, Intranasal, IV Infusion
- Tasteless, Non-Irritating to Mucosa
- Now available as a generic
- Produces ‘rousable sedation’ – exhibiting many properties similar to natural sleep
- Pregnancy category C
- Complete biotransformation in liver
- IV terminal elimination half-life 2 hours

Patients woke easily with cognition from a sedated state
- Quick recovery
- More amnesia than a comparable dose of propofol
- Minimal influence on respiration and circulation

- Many patients may benefit from adding midazolam to the technique
- Increasing the maintenance infusion may allow the dental procedure to start earlier
Dental-specific Studies

- Dexmedetomidine sedation with and without midazolam for third molar surgery
  - Smiley MK, Prior SR 61:3;2014
- A comparison of Dexmedetomidine sedation with and without midazolam for dental implant surgery

*IV Dex alone showed a slower onset and unpredictable sedative and amnestic response than more common anesthesia alternatives

Rationale for Continuous Infusion

- Enhanced cardiovascular stability
- Enhanced respiratory stability
- Minimize fluctuations in drug serum concentration
- Smoother intraoperative course
- Less patient movement
- Utilize less drug
- More rapid recovery

Bennett JOMFS 1998
Continuous Infusion
What Works Well?

**Propofol – Ideal Pharmacokinetics**

**GA**

- **Induction**
  - Adult: 1.25 mg/kg
  - Peds: 2.5-3.5 mg/kg
- **Maintenance**
  - Adult: 100-200 mcg/kg/min
  - Peds: 125-300 mcg/kg/min

*Minimize infusion dose to optimize recovery times*

**MAC**

- **Induction**
  - Injection: 0.5 mg/kg
  - or 50-100 mcg/kg/min
- **Maintenance**
  - 25-150 mcg/kg/min

Continuous Infusion
What Works Well?

**Remifentanil – Ideal Pharmacokinetics**

- Add remifentanil to propofol infusion (1:500) to quicken recovery, use less drug

  Lacombe JOMFS 2006

**Dexmedetomidine**

Best current office-based use may be low-dose infusion to minimize/avoid emergence delirium

Continuous Infusion
Less Ideal!

**Ketamine**

- Metabolism to norketamine, an active metabolite
- Norketamine - 1/3-1/5 as potent and contributes to prolonged effects, especially with intravenous infusion


- No statistical significance in respiratory stability, satisfaction, PONV
- Ketamine group – prolonged recovery
Characteristics of an ‘Ideal’ anesthetic Agent

- Sufficient Potency
- Non-Flammable
- Non-pungent - Bronchodilator
- No Adverse Respiratory Complications
- No Adverse Cardiac Complications
- Provide Muscle Relaxation
- Minimal Metabolism
- No Postemergence Side Effects (EA)
- Reliable and Simple Delivery System
- Economical

VOLATILE ANESTHETICS

Low Blood Gas Solubility Confers Many Clinical Advantages!

- Rapid Onset
- Greater Control & Precision of Depth
- Rapid Recovery
- Rapid Return of Airway Reflexes

McKay: Anesth Analg 2005

Desflurane > Sevoflurane > Isoflurane > Halothane

<table>
<thead>
<tr>
<th>Properties</th>
<th>Halothane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling Point</td>
<td>50</td>
<td>48.6</td>
<td>22.8</td>
<td>58.6</td>
</tr>
<tr>
<td>Pungency</td>
<td>Excellent</td>
<td>Poor</td>
<td>Marked</td>
<td>Excellent</td>
</tr>
<tr>
<td>Blood Gas Solubility</td>
<td>2.3</td>
<td>1.4</td>
<td>0.42</td>
<td>0.66</td>
</tr>
<tr>
<td>MAC 100% O₂</td>
<td>0.77</td>
<td>1.15</td>
<td>6</td>
<td>2.05</td>
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<tr>
<td>Metabolism</td>
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<td>0.02%</td>
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MAC: MINIMUM ALVEOLAR CONCENTRATION

‘Concentration of inhaled anesthetic agent that prevents movement in response to skin incision in 50% of subjects at sea level in 100% oxygen’

- Alveolar concentration can be easily measured
- Weight & Anesthetic duration do not alter MAC
- Doses of anesthetics in MACs are additive
- MAC highest at age 6 months, then declines

FACTORS AFFECTING MAC

<table>
<thead>
<tr>
<th>INCREASES MAC</th>
<th>DECREASES MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEDIATRICS</td>
<td>NITROUS OXIDE</td>
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<tr>
<td>HYPERCAPNEA</td>
<td>CNS DEPRESSANTS</td>
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<tr>
<td>HYPERThERMIA</td>
<td>HYPOCAPNEA</td>
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<td>ALTITUDE</td>
<td>HYPOTHERMIA</td>
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VOLATILE ANESTHETICS

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VOLATILE ANESTHETICS

Respiratory Depressant Effect
- Sevoflurane
- Isoflurane
- Desflurane

Bronchodilating Effect
- Sevoflurane
- Isoflurane
- Desflurane

*Least to Greatest
*Greatest to Least

SEVOFLURANE INDUCTION PROCEDURE: COMPARISON between FIXED 8% vs INCREMENTAL TECHNIQUE in PEDIATRIC PATIENTS

100 children
Both groups premedicated with midazolam 0.5mg/kg
1. Sevo at 1% N₂O 50%-increased sevo by 1% every 3 breaths for induction
2. Sevo 8% N₂O 50% induction
Time to LOC lower using 8% method
Incremental method cost almost half of fixed 8% induction method

Singh PM
AANA Journal 82:2014

SEVOFLURANE vs PROPOFOL for ANESTHETIC INDUCTION: A META-ANALYSIS

- 12 included studies
- Time to LOC was similar
- More frequent apnea in propofol group
- Induction complications similar
- Time to successful LMA insertion similar
- Success with LMA first attempt higher in sevoflurane group
- PONV more significant in sevoflurane group

Joo H
Anesth Analg 91:2000
SEVOFLURANE vs PROPOFOL for INDUCTION and MAINTENANCE of ANAESTHESIA with the LARYNGEAL MASK AIRWAY in CHILDREN

Study of 120 children
Propofol 3mg/kg induction
5mg/kg/hr maintenance group
Sevoflurane 7% induction
1.7% maintenance group
LMA insertion time shorter with sevoflurane group
Heart rate higher in the sevo group
Emergence more rapid with sevo group
Emergence agitation increased with sevoflurane group

Lopez Gil M
Ped Anes
9:1999

WHAT is EMERGENCE AGITATION?

Children aroused from anesthesia enter a state of excitation...

- Irritable, uncompromising, uncooperative, incoherent, crying
- Do not recognize familiar people, objects
- Combative behavior
- Occurs within 30 min of recovery
- Often resolves spontaneously

EMERGENCE AGITATION RISK FACTORS

CHILDREN...
MORE EMOTIONAL
LESS SOCIAL
MORE IMPULSIVE
LESS ADAPTABLE

PARENTS...
HIGH ANXIETY

PREOPERATIVE ANXIETY
DISTRESS DURING INDUCTION
PREVIOUS TRAUMATIC EXPERIENCE AT DENTIST
POOR PAIN CONTROL
HEAD & NECK PROCEDURES

PRESCHOOL AGE: 2-6
BOYS > GIRLS
PREOPERATIVE ANXIETY
DISTRESS DURING INDUCTION
PREVIOUS TRAUMATIC EXPERIENCE AT DENTIST
POOR PAIN CONTROL
HEAD & NECK PROCEDURES

45

46

47
EFFECTS OF EMERGENCE AGITATION

- Injury to the child
- Injury to the surgical site
- Inability to control bleeding
- Accidental removal of dressings
- Accidental removal of IV catheters
- May require additional nursing care
- May require supplemental sedatives/analgesics
- Raises questions about anesthetic ‘quality’
- Causes anxiety in parents witnessing EA

PHARMACOLOGICAL PREVENTION of SEVOFLURANE and DESFLURANE RELATED EMERGENCE AGITATION in CHILDREN: A META-ANALYSIS of PUBLISHED STUDIES

- 324 studies identified
- 58 relevant articles
- 37 studies included
- 3172 total patients
- Randomized studies
- Double-blinded studies
- Control group
- Standardized definition of EA

Dahmani S
Brit J Anaes
104:2010

TREATMENTS STUDIED for PROPHYLACTIC PREVENTION of EA

- Midazolam
- Propofol
- Fentanyl
- Ketamine
- α2-Agonist
- Local anesthesia
- Ondansetron
### PROPHYLACTIC TREATMENT of EA

**Midazolam**
- Premedication – **not protective** against EA
- Bolus after induction – **not protective** against EA

**Propofol**
- Continuous infusion – **protective** against EA
- Bolus at end of case – **protective** against EA
- Bolus after induction – **not protective** against EA

**Ketamine**
- Premedication – **protective** against EA
- Bolus after induction – **protective** against EA
- Bolus at end of case – **protective** against EA

---

**Fentanyl**
- Intranasal – **protective** against EA
- Bolus after induction – **not protective** against EA

**α₂-Agonist – Dexmedetomidine/Clonidine**
- All routes/timing – **protective** against EA

**Local anesthesia**
- **Protective** against EA

**Ondansetron**
- **Not protective** against EA
- Only 2 studies – more research needed

---

### EVIDENCE-BASED CONCLUSIONS

Reduce/Eliminate Emergence Agitation & Prevalence of Nausea/Vomiting to attain Ideal Pediatric Anesthetic Experience

**Premedication:** Midazolam 0.5mg/kg
- Dexmedetomidine: 3-4mcg/kg

**Induction:** Sevoflurane: Incremental to 8%

**Maintenance:** Sevoflurane 1.5-3%

**Emergence:** Propofol 0.5-1mg/kg
**Xenon Anesthesia**

- Originally discovered in 1939 by Behnke and Yarborough of the US Navy
- Lawrence published experiments in 1946
- Lachmann, Erdmann and rediscovered it in 1990
- Multi-center clinical trials have been completed in the European Union
- Noble gas found in very small concentrations (0.0000087) in the air
- Manufactured by fractional distillation of liquified air - expensive

**Xenon Anesthetic Gas**

Fulfills many of the ideals of an anesthetic gas...

- Lowest blood gas solubility (0.12)
- MAC = 0.63, 1.5x more potent than \( \text{N}_2\text{O} \)
- Non-flammable
- Absence of metabolism
- Low toxicity
- Void of teratogenicity
- Produces highest regional flow in the brain, liver, kidney and intestine
- No cardiovascular depression

**Xenon and the Global Environment**

- Volatile anesthetics and \( \text{N}_2\text{O} \) contribute to the greenhouse effect
- \( \text{N}_2\text{O} \) is 230x more potent as a greenhouse gas than \( \text{CO}_2 \)
  - \( \text{N}_2\text{O} \) as a waste anesthetic contributes 0.1% of global warming
- Xenon adds no atmospheric pollution
- Xenon does not deplete the ozone layer
Xenon Anesthetic Gas

- Because of its rarity and expense, waste must be reduced to an absolute minimum
- Given via a rebreathing system using the lowest possible gas flow
- Closed loop feedback control mechanism delivers only the amount needed to maintain constant gas concentration and volume

Muscle Relaxants

**Depolarizing** – Mimics action of Ach
- Succinylcholine

**Nondepolarizing** – Interferes with Ach
- Long Acting
  - Pancuronium
- Intermediate Acting
  - Vecuronium Atracurium
  - Rocuronium Cisatracurium
- Short Acting
  - Mivacurium

### Muscle Relaxants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Intubating Dose mg/kg</th>
<th>Infusion mcg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>1</td>
<td>4</td>
<td>2-3</td>
<td>2</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>1-2</td>
<td>20-35</td>
<td>0.6-1.2</td>
<td>--</td>
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<tr>
<td>Mivacurium</td>
<td>2-3</td>
<td>12-20</td>
<td>0.25</td>
<td>5-6</td>
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<tr>
<td>Atracurium</td>
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<td>20-35</td>
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<tr>
<td>Cisatracurium</td>
<td>3-5</td>
<td>20-35</td>
<td>0.1</td>
<td>1-1.5</td>
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<tr>
<td>Vecuronium</td>
<td>3-5</td>
<td>20-35</td>
<td>0.08-0.1</td>
<td>1</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>3-5</td>
<td>60-90</td>
<td>0.1</td>
<td>--</td>
</tr>
</tbody>
</table>
### Succinylcholine: Pros & Cons

- Trigger for Malignant Hyperthermia
- Only Emergencies for peds, not elective use
- Bradycardia with first dose
- Hyperkalemia possible
- Fasiculations and Masseter Spasm
- Consider Defascication Dose of tubocurarine
- Postop Myalgias
- Bronchospasm / Histamine release
- Increased Intraocular / Intragastric Pressure
- Redosing can result in dysrhythmias

### Sugammadex (Bridion)

- Gamma-cyclodextrin ring shaped molecule which reverses the effects of neuromuscular blocking agents rocuronium and vecuronium by encapsulation in the plasma not at the neuromuscular junction
- Lack of cardiovascular side effects
- Reduces effectiveness of BCPs for 7 days

### Sugammadex

#### Level of NMB with rocuronium or vecuronium

<table>
<thead>
<tr>
<th>Dose of BRIDION</th>
<th>Example dose of BRIDION for a patient weighing 80 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg/kg</td>
<td>160 mg (5.6 mL)</td>
</tr>
<tr>
<td>4 mg/kg</td>
<td>320 mg (5.2 mL)</td>
</tr>
</tbody>
</table>

Use after immediate administration of rocuronium:

16mg/kg – Cost: $114 per 200mg

Recovery 3 times faster than neostigmine
Sugammadex

Precautions

• Angioedema
• Hypersensitivity
• Infection
• Anaphylaxis

Warnings/Precautions

- Sugammadex has a high sensitivity to blood and is contraindicated in patients with a history of hypersensitivity to the medication.
- Use with caution in patients with a history of cardiovascular disease, as sugammadex can cause marked decreases in arterial pressure.

Contraindications

- Sugammadex is contraindicated in patients with a history of anaphylaxis or severe allergic reaction to sugammadex.

Kovanaze Nasal Spray

- 3% tetracaine hydrochloride & 0.05% oxymetazoline hydrochloride intranasal spray
- Used for regional maxillary pulpal anesthesia of incisors, canines, and 1st premolars
- FDA approved for adults and children >40kg
- Tetracaine HCl 6mg & Oxymetazoline HCl .1mg (each .2ml spray)

Kovanaze Nasal Spray

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥18 years old)</td>
<td>2 sprays (0.2 mL per spray), 4 to 5 minutes apart&lt;br&gt;1 additional spray (0.2 mL per spray) if local anesthesia has not been achieved 10 minutes after the second spray</td>
</tr>
<tr>
<td>Children who weigh 40 kg or more</td>
<td>2 sprays (0.2 mL per spray), 4 to 5 minutes apart</td>
</tr>
</tbody>
</table>
Kovanaze Nasal Spray

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension/thyroid disease</td>
<td>May increase blood pressure</td>
<td>Monitor blood pressure. Not recommended for patients with inadequately controlled hypertension or thyroid disease.</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>May contribute to nasal bleed</td>
<td>Not recommended for patients with history of frequent nose bleeds (5 or more per month). Monitor susceptible patients closely.</td>
</tr>
<tr>
<td>Oedema</td>
<td>Congestion of difficulty swallowing</td>
<td>Carefully monitor</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>May cause methemoglobinemia, particularly when used with methemoglobin-inducing agents</td>
<td>Not recommended for patients with history of congenital or idiopathic methemoglobinemia.</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Common symptoms of anaphylaxis: urticaria, angioedema, bronchospasm, shock</td>
<td>Seek emergency help</td>
</tr>
</tbody>
</table>

Local Anesthesia - Ropivacaine

- Long-acting Aminoamide Anesthetic
- Clinically similar to Bupivacaine
- Fewer Cardiac and CNS Adverse Effects  
  Knudsen 1997
- More Rapid Onset of Anesthesia Than Bupivacaine
- Ropivacaine Concentrations Cause Vasoconstriction
- 0.50%-0.75% Produce Adequate Dental Anesthesia  
  El-Sharrawy 2006

Exparel (1.3% liposomal bupivacaine)

- Multiple phospholipid bilayers with an aqueous core that increases stability of liposome and extends drug release
- FDA approved for single dose intraoral infiltration the surgical site not for nerve blocks
- Clinical trials adult maximum dose: 20ml (260mg)
- Not FDA approved for patients <18 or pregnant
Exparel (1.3% liposomal bupivacaine)

- Injected as small aliquots, infiltrating the surgical area
- Avoid administration of non-bupivacaine local anesthetics less than 20 minutes prior to injecting Exparel to avoid disruption of liposomes
- Avoid administration of immediate release bupivacaine and other local anesthetics for 96 hours after Exparel infiltration to avoid unintentional overdose (wristband)

HTX-011
Extended Release Bupivacaine/Meloxicam

- 72 hours of analgesia
- Reduces need for opioids
- 'Biochronomer' technology
- Meloxicam reduces local inflammation
- Reverses the acidic environment in the surgical site
- Potentiates bupivacaine

HTX-011
Extended Release Bupivacaine/Meloxicam

- Studied in:
  - Hernia Repair
  - Abdominoplasty
  - Bunionectomy
  - Total Knee Arthroplasty
  - Breast Augmentation

  - FDA Fast Track Designation
    - 4th Qtr 2017
  - Breakthrough Therapy Designation
    - 2nd Qtr 2018
  - Submitted an NDA to FDA
    - December 2018
Questions???