Wake Up! The Evolution of Intubation and General Anesthesia Reversal Agents
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Live Activity Handout
4 slides per page
Wake Up! The Evolution of Intubation and General Anesthesia Reversal Agents

ACTIVITY DESCRIPTION
This activity is intended for health-system pharmacists and nurses. On this journey through the process of intubation to extubation & we will review the process of intubation and discuss the most commonly utilized drugs and the rationale behind their use to include etomidate, benzodiazepines, neuromuscular blockers, propofol and ketamine. Now that the patient is intubated, we must keep them sedated until extubation. Common sedation medications such propofol, benzodiazepines and dexmedetomidine will be examined. Finally we must wake up and extubate the patient. We will discuss the most commonly used drugs for the reversal of medications used during the intubation process including an in depth look at the reversal of neuromuscular blockade. We will compare sugammadex to the current standard reversal medication and discuss its potential impact on patient care.

TARGET AUDIENCE
The target audience for this activity is pharmacists and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:
• Review the process of intubation and medications used in the intubation process
• Outline medications used for ventilator sedation once intubated
• Identify medications and clinical practice pearls associated with the reversal of anesthesia (patient wake up process)
• Describe the advantages and disadvantages of the neuromuscular blockade reversal agents with regards to clinical challenges and impact on patient care

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Objectives

- Review the process of intubation and medications used in the intubation process
- Outline medications used for ventilator sedation once intubated
- Identify medications and clinical practice pearls associated with the reversal of anesthesia/sedation
- Describe the advantages and disadvantages of the neuromuscular blockade reversal agents with regards to clinical challenges and impact on patient care

Rapid Sequence Intubation

- Simultaneous administration of a potent sedative agent and a neuromuscular blocking agent for the purpose of endotracheal intubation
- The process of establishing an advanced airway
  - Surgery utilizing medications that cause respiratory depressor or paralysis
  - Respiratory compromise
    - Aspiration
    - Acute Respiratory Distress Syndrome (ARDS)
- Airway protection
  - Anaphylaxis
  - Angioedema

Intubation

- Common types:
  - Endotracheal
    - Nasal
    - Otracheal
  - Tracheostomy
  - Cricothyrotomy
    - Last resort where traditional intubation is impossible or contraindicated
    - Foreign body
    - Severe angioedema
Intubation

- **Process:**
  - Medications given to sedate and paralyze both the patient and gag reflex to reduce aspiration
    - Sedate before you paralyze!!!
  - Laryngoscope used to directly view the larynx
  - Endotracheal tube passed through vocal cords into the trachea
  - Tube advanced to sit just above the carina
  - Tube secured via holder or taped in place
  - Tube placement verified:
    - Breath sounds
    - Chest x-ray
    - End tidal CO₂

Etomidate (Amidate)

- Short acting non-barbiturate general anesthetic
  - Has sedative and hypnotic properties
- **Induction agent**
  - Onset: <60 seconds
  - Duration: 2-10 minutes
  - Pregnancy category: C
- **Indications:**
  - Need for rapid induction
  - Hypotensive patient

Etomidate (Amidate)

- **Intubation dose:** 0.3 mg/kg
- **Major adverse effects:**
  - Spontaneous myoclonus (33%)
  - Adrenal suppression
    - Likely avoid in septic shock
  - Vomiting

Propofol (Diprivan)

- To be discussed in depth later in presentation
- **Indications:**
  - Seizures
  - Head trauma
  - Malignant hyperthermia
  - Frequent neurological monitoring required
- **Intubation dose:** 0.5-3 mg/kg
- **Major adverse effects:**
  - Hypotension
**Ketamine (Ketalar)**

- NMDA receptor antagonist
  - Derivate of PCP
  - Modulates central sensory processing
  - Onset: 30-60 seconds
  - Duration: 10-15 minutes
  - Pregnancy category: Unknown
- Indications:
  - Well tolerated in children
  - Hypotensive patient
  - Patients with pre-existing bronchospasm

**Ketamine (Ketalar)**

- Intubation dose: 1-2 mg/kg
- Major adverse effects:
  - Hallucinations/nightmares
  - Can be decreased by benzodiazepines and clonidine
  - Increase in intracranial pressure
  - Hypertension
  - Tachycardia

**Benzodiazepines**

- Midazolam (Versed) primarily used
- Enhance the inhibitory effects of GABA
  - Onset: 1-5 minutes
  - Duration: 30-60 minutes
  - Longest acting induction agent
  - Pregnancy category: D
- Indications:
  - Can be used in any patient unless allergy to benzodiazepine
- Intubation dose: 0.3-0.35 mg/kg

**Benzodiazepines**

- Major adverse effects:
  - Hypotension
  - Respiratory depression
  - Only induction medication recommended that causes significant respiratory depression
Lidocaine/Benzocaine

- Useful adjunctive medication
- Used to blunt transient increases in ICP seen with rapid sequence intubation
- Indications:
  - Multi-trauma
  - Head injury patients
- No solid data supporting its use
- Induction dose:
  - Lidocaine: 1.5 mg/kg IV
  - Benzocaine: spray prior to intubation

Major adverse effects:
- Risk of methemoglobinemia
  - Low risk
- Low risk for cardiovascular effects
  - Arrhythmias
  - Hypotension

Neuromuscular Blocking Agents

- Depolarizing neuromuscular blockers
  - Mimic the action of acetylcholine at binding sites causing depolarization
  - More resistant to acetylcholine esterase preventing repolarization
  - Succinylcholine most commonly used of this class
- Non-depolarizing neuromuscular blockers most commonly used
  - Block acetylcholine from binding to receptors on the motor end plate inhibiting muscle depolarization
  - More resistant to acetylcholine esterase preventing repolarization
  - Inhibit depolarization of all skeletal muscle including diaphragm which inhibits respiration

- Rocuronium and vecuronium are 2 most commonly used in the OR setting
- Uses
  - Rapid sequence intubation
    - Rocuronium, succinylcholine (Anectine, Quelicin), vecuronium
    - Cisatracurium (Nimbex) not indicated due to prolonged onset of action
  - OR
    - Rocuronium, succinylcholine, vecuronium, pancuronium
    - Ventilator paralysis
      - Vecuronium, cisatracurium, rocuronium
Neuromuscular Blocking Agents

- RSI dosing
  - Succinylcholine: 1-1.5 mg/kg
    - T1/2=15 min
  - Common adverse effects
    - Hyperkalemia
    - Malignant hyperthermia
  - Vecuronium: 0.08-0.1 mg/kg
    - T1/2=45 min
  - Rocuronium: 0.6-1.2 mg/kg
    - T1/2=30 min
  - Common adverse effects
    - Hypersensitivity reactions

Staying Asleep!

2013 PAD Guidelines

- Recommend maintaining light levels of sedation unless clinically indicated
  - Improved clinical outcomes
    - Shorter duration of mechanical ventilation
    - Decreased ICU length of stay (LOS)
- Monitoring depth of sedation and brain function
  - Richmond Agitation-Sedation Scale (RASS)
  - Sedation Agitation Scale (SAS)
  - Bispectral index scale (BIS) no longer recommended at primary
    - Objectives scales only to be used as adjunct

2013 PAD Guidelines

- Medications for sedation:
  - 1st line: Non-benzodiazepines
    - Propofol (Diprivan)
    - Dexmedetomidine (Precedex)
  - 2nd line: Benzodiazepines:
    - Midazolam (Versed)
    - Lorazepam (Ativan)
  - 2nd line for most patients
  - Propofol and Midazolam remain the workhorse sedation drugs

★ • Goal: Get to sleep fast and wake up as soon as possible!
**Propofol (Diprivan)**

- Short acting hypnotic with a poorly defined mechanism of action.
  - GABA antagonism, NMDA receptor blockade?
- Lipid emulsion
- Highly lipophilic with a large volume of distribution
  - Very rapid CNS penetration
- Very attractive pharmacokinetics
  - Onset: 10-50 seconds
  - Duration: 3-10 min
- Will not accumulate in patients with renal or hepatic impairment

**Propofol (Diprivan)**

- Very useful in sedating acute trauma patients or patients with head injury
  - Useful in determining neurological status
  - Lowers intracranial pressure
  - Does have anticonvulsant properties
- Ventilator sedation dosing:
  - 5-25 mcg/kg/min usual starting rate but can vary by protocol
  - Usually titrate by 5-10 mcg/kg/min every 3-5 minutes until reached desired level of sedation reached
  - No generally accepted maximum dose with data up to 200 mcg/kg/min

**Propofol (Diprivan)**

- Adverse effects:
  - Egg, Chicken, Soybean or Glycerin allergy
  - Cardiovascular:
    - Pronounced hemodynamic side effects
    - Can decrease blood pressure ≥ 30%
    - Hypotension is dose and rate related
    - Increased clearance of catecholamines
    - Bradycardia
    - Negative inotrope
    - Triglyceride Induced Pancreatitis
    - Propofol Infusion Syndrome (PRIS)

**Dexmedetomidine (Precedex)**

- Alpha<sub>2</sub> agonist
- Activity:
  - Locus caeruleus of the brain stem
    - Reduces sympathetic activity and level of arousal
    - Produces a different type of sedation
  - Dorsal horn of the spinal cord
    - Inhibit the firing of nociceptive neurons
    - Inhibit the release of substance P
    - Blunted response to pain
- Causes no respiratory depression so can be used w/o vent!
Dexmedetomidine (Precedex)

- Decreased opiate requirements
- Newer data showing decreased incidence of delirium post extubation
- Has been shown to increase # of ventilator free days
  - Dexmedetomidine vs. midazolam = 41 hours (p=0.03)
  - Dexmedetomidine vs. propofol = 21 hours (p=0.24)
- Conflicting data on ICU LOS
- Dosing
  - 1 mcg/kg infused over 10 minutes
  - 0.2-0.7 mcg/kg/hr maintenance with max dose of 1.5 mcg/kg/hr
  - Must wean to avoid withdrawal syndrome

Midazolam (Versed)

- Most commonly used benzodiazepine for ventilator sedation
- More lipid soluble compared to lorazepam
  - Faster onset of action
  - Larger $V_d$ which can cause a longer awakening time even though shorter duration of action
- No risk of propylene glycol toxicity
- Pharmacokinetics:
  - Onset: 3-5 min
  - $T_{1/2}$: 2-6 hrs
  - Caution if SBP<90 or HR<60

Midazolam (Versed)

- Usual soft max of 20 mg/hr but will vary between institution
- Can be administered as a continuous infusion or intermittent bolus dosing.
- Can accumulate in patients with renal or hepatic disease prolonging extubation

Neuromuscular Blockers

- Continuous infusions:
  - Acute respiratory distress syndrome (ARDS)
  - Lack of synchronization between patient/ventilator
  - Severe multi-trauma
  - Succinylcholine not used
- Dosing:
  - Vecuronium: 0.8-1.7 mcg/kg/min
  - Rocuronium: 8-12 mcg/kg/min
  - Cisatracurium: 0.5-10 mcg/kg/min
Reversal of Neuromuscular Blockers

- Reversal of neuromuscular blockade can be a challenging endeavor
- Typical reversal:
  - Neostigmine (Bloxiverz)
    - Acetylcholinesterase inhibitor
  - Glycopyrrolate (Robinul)
    - Muscarinic antagonist
  - Limited efficacy of combination especially in profound neuromuscular blockade
  - Suboptimal side effect profile
  - Increased incidence of cardiac arrhythmias

Neostigmine (Bloxiverz)

- Allows acetylcholine to bind to receptor and facilitates muscle depolarization and the ability to spontaneously breathe
- Neostigmine dosing based on NMB given:
  - Rocuronium: 0.03 mg/kg
  - Vecuronium/Pancuronium: 0.07 mg/kg
  - Max dose = 5 mg total dose
- Adverse effects
  - Bradycardia!
  - Convulsions
  - Diarrhea!
  - Increased salivation

Glycopyrrolate (Robinul)

- Blocks the action of acetylcholine in smooth muscle, salivary glands and CNS
- Given to antagonize the cholinergic effects of neostigmine
- Dosing:
  - 0.2 mg x each mg of neostigmine given
- Adverse reactions:
  - CNS effects
  - Xerostomia
  - Urinary retention
Challenges of NMB Reversal

- Needs:
  - Effective neuromuscular blocker reversal agent (complete reversal)
  - Neuromuscular blockers to be given throughout the procedures or for longer times during intubated periods
  - Expanded surgical use
  - Reduced side effects post-op
  - Reduced use of succinylcholine
    - Malignant hyperthermia
    - Hyperkalemia
  - Decreased residual paralysis post-op
  - Shorter PACU LOS and faster discharge post-op

Sugammadex (Bridion)

- 1st in its class novel agent (U.S. approval Dec. 2015)
- Longer history of use in Europe and in over 70 countries worldwide
- Cyclodextrin molecule that binds to and encapsulates non-depolarizing neuromuscular blocking agents preventing its action
- High affinity for rocuronium and moderate affinity for vecuronium/pancuronium
- Inactive against non-steroidal neuromuscular blockers
  - Succinylcholine and cisatracurium

Sugammadex (Bridion)

- Avoids the use of acetylcholinesterase inhibitors and anti-muscarinic drugs
- Pharmacokinetics
  - T\textsubscript{1/2}: 2.2 hrs
  - Low plasma protein binding
  - Not metabolized in the body
    - Few known drug-drug interactions due to no induction or inhibition of cytochrome p-450 enzymes
  - Renally eliminated unchanged
- Dosing: utilizing actual body weight
  - Profound blockade: 4 mg/kg
  - Moderate blockade: 2 mg/kg

Sugammadex- Advantages

- Complete neuromuscular blockade reversal regardless of depth
- Complete reversal usually within 3 minutes
  - Much faster than current reversal agents
    - Moderate neuromuscular blockade
    - Rocuronium w/ sugammadex vs. neostigmine (1.5 min vs. 18.5 min) p<0.0001
    - Jones et. al
  - Deep neuromuscular blockade
    - Rocuronium w/ sugammadex vs. neostigmine (2.9 min vs. 50.4 min) p<0.0001
Sugammadex - Limited Data

• Very little data regarding the reversal of continuous infusions of neuromuscular blockers
  • Must extubate scenario
  • Residual paralysis postponing extubation

Addressing Challenges

• Sugammadex advantages continued:
  ★• Less adverse effects as compared to neostigmine and glycopyrrolate
  • No hepatic or renal dose adjustments
  • Allows expanded use of non-depolarizing agents for rapid sequence intubation
  • Possibly less use of Succinylcholine
    • Hyperkalemia
    • Malignant hyperthermia
  • Proven faster complete reversal of blockage and faster to normal train of four
    • Quicker out of the OR and quicker out of PACU

Sugammadex - Disadvantages

• Risk of hypersensitivity reactions
  • Usually occurs within 4 minutes of administration and with higher dosing strategies
  • Synergistic mechanism with Rocuronium?
  • Main reason for initial US FDA rejections and delay to market
  • Reported reactions mainly consisting of case reports and limited data from clinical trials
  • Potential role for skin testing?

Sugammadex

• Disadvantages continued:
  ★• Hormonal contraceptives
    • Interaction with all hormonal contraceptives
    • Causes decreased serum progesterone levels
    • Alternative non-hormonal contraception recommended for 7 days after administration
  • Product Cost!
    • Economic studies shown that to offset costs, the drug must ideally reduce both OR and PACU time
    • Cost of reintubation for desaturation post extubation
    • Cost of malignant hyperthermia/hyperkalemia treatment with succinylcholine
**Sugammadex- Cost Considerations**

- **Unal et al.**
  - Turkish study evaluating cost difference between Rocuronium reversal post-op with Sugammadex vs. neostigmine
  - Reversal with Sugammadex was 2x more expensive than neostigmine
  - Decreased OR time: (72 vs. 96 min, p<0.001)
  - Decreased PACU time: (23 vs. 37 min, p<0.001)
  - Complication treatment cost with neostigmine reversal represented a 19.7x cost increase
    - Statistically significant reductions
      - Respiration-related complications
      - Total hemodynamic related complications
      - Re-intubations and airway manipulations

**Sugammadex- Appropriate Candidates**

- **Indications:**
  - When immediate reversal of neuromuscular blockade is required
    - “Cannot intubate, cannot ventilate”
    - Cholinesterase inhibitor failure
    - Difficult airway cases:
      - Morbid obesity
      - Elderly
      - Existing respiratory co-morbidities
    - Renal failure with vecuronium/pancuronium metabolites
    - Early completion or cancellation of surgery
    - Intraoperative hyperthermia
    - Pre-existing neuromuscular disease

**Flumazenil (Romazicon)**

- Reversal agent for all benzodiazepines
- Quickly reverses even deep levels of sedation
- Competitively inhibits the activity of the drug at the benzodiazepine receptor site on the GABA/benzodiazepine receptor complex
- Dosing: 0.2 mg IV push over 15 seconds
  - Can repeat 0.2 mg dose every minute until reversal of sedation to max dose of 1 mg
- Can precipitate a withdrawal syndrome in chronic users
  - Med history is important

**Take Home Points**

- Anesthesia is very provider specific!
- Many options for sedation prior to intubation and all relatively equivalent
- Non-benzodiazepines remain 1st line ventilator sedation meds but propofol and midazolam will remain workhorse drugs in clinical practice
- Residual neuromuscular blockade/sedation increases costs!
  - Longer OR/PACU/ICU time
  - More failed extubations leading to longer ventilator time and prolonging hospital LOS
- Prompt sedation reversal can improve patient outcomes!