ANESTHESIA

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Overview

- A commonly used regimen involves sedation with the benzodiazepine, Midazolam, followed by induction with Propofol.
- Both agents are synergistic with opioids. Fentanyl is the opioid generally employed.
- Neuromuscular blockade follows both to permit intubation as well as to maintain immobility.
- The non-depolarizing agent, Ruroconium, is often employed if deep anesthesia is desired.
- Sevoflurane inhaled anesthetic gas is commonly employed.

Sedation and anesthesia

- Deep sedation
- Patient is arousable
- Deep anesthesia
- Patient is nor arousable
- Deep sedation may require intubation to maintain airway control

Sedation and anesthesia

- Midazolam
- Benzodiazepine
- Effective in 1.5 minutes if given with opioid; 2.5 minutes if no opioid
- Diminishes mean arterial pressure, cardiac output, systemic vascular resistance
- $t_{½}$ is 3 hours
- Metabolized in liver (Cytochrome 3A4)
- Induces amnesia

Sedation and anesthesia

- Fentanyl
- Opioid agonist
- 0.1mg equivalent to 10mg morphine
- Distributes in minutes
- Accumulates in fat and skeletal muscle
- Transformed in liver
- $t_{½}$ is 3 hours
- 30-60 minutes of analgesia
- Diminishes sensitivity to CO_2 stimulation; effect longer than respiratory depression

Intravenous anesthetics

- Propofol
- Dose dependent activation (generally within one minute).
- Protein bound
- Oxidized in liver
- 40% renal excretion.
- Biphasic distribution, with a $t_{½}$ of 7 hours
- Crosses the placenta.
- GABAA and NMDA receptor agonist
- Diminished Ca2+ influx (voltage channel)

Intravenous anesthetics

- 15-40% fall in blood pressure (due to fall in vascular resistance as well as diminished sympathetic activity).
- Low incidence of bronchospasm.
- Lipidemic.
- Egg and soy based lecithin. May lead to allergic reaction.

Intravenous anesthetics

- Prolonged infusion (<24 hours) of propofol associated with a syndrome of acidosis, bradycardia, hyperlipidemia, and rhabdomyolosis
- Electron transport function impaired in mitochondrion
- Inhibit entry of long chain fatty acid into cell
- Very low frequency (δ) waves, tightly bunched, on EEG

Intravenous anesthetics

- Dexmedetomidine
- Analgesia, anxiolysis, light sedation
- α_2 receptor agonist
- Decrease noradrenegic neurons in locus ceruleus
- Downstream inhibition of GABA neurons in ventrolateral preoptic nucleus
- Elimination $t_{½}$ 2-3 hours
- Metabolized by glucuronidation and CYP2A6 oxidation

Intravenous anesthetics

- Less respiratory depression or amnesia than with benzodiazepines (mimics Stage 2 sleep)
- Less delerium
- Adjunct to opioids as analgesic at spinal cord level
- For use in ICU

Intravenous anesthetics

- Ketamine
- Non-competitive NMDA receptor agonist
- Disrupts glutamate metabolism
- Induces dissociative state (sedation, amnesia, pain relief)
- Preserves breathing and airway reflexes
- Increases blood pressure, contractility, cerebral blood flow
- Moderate bronchodilator
- Alternating high frequency γ and very low frequency δ waves on EEG

Anesthetic gases

	Effective MAC	Blood/Brain partition coefficient	Effects
Halothane	0.75	2.9	Hepatotoxic; May cause malignant hyperthermia in patients with ryanodine receptor or dihydropyridine receptor abnormality (Ca^{2+} accumulates in muscle cytosol)
Isoflurane	1.2	2.6	Purging may lead to bronchospasm; pungent
Desflurane	6.6	1.3	Purging may lead to bronchospasm; pungent; Hypertension if administered rapidly; may lead to CO toxicity
Sevoflurane	2.6	1.7	Cleared rapidly

Mean alveolar concentration

- MAC is the percentage of gas concentration needed to provoke immobility to noxious stimuli in 50% of patients
- All anesthetics augment GABA signaling, leading to diminished neuronal firing
- All diminish systemic vascular resistance
- All diminish acute hypoxic response
- MAC measured at anesthetic machine (wavelength of particular gas)
- Level relates to speed of induction

Mean alveolar concentration

- MAC declines by 6% per decade after age 40
- Highest sensibility at 6-12 months of age
- When MAC >0.4, patient is amnesic (no recall)
- At MAC 1.0, 50% of population anesthetized
- 1.2, 95%
- 1.3, 99.7%

- If the dry absorber (removing CO_2) is not changed frequently, CO accumulates

Nitrous oxide analgesia

- Nitrous oxide is analgesic
- Has sympathetic effect that offsets myocardial depression of anesthetic gases
- Diffuse hypoxia when discontinued
- Must flush with 100% O_2
- Blocks Vitamin B_{12} recycling
- Non-volatile
- Inhibit NMDA receptors as well as gluatamate signaling

Nitrous oxide analgesia

- MAC 0.75%, with a blood/brain partition coefficient of 1:1
- Rapidly distributed from CNS
- Metabolized in liver
- Contraindicated in bowel, brain, middle ear, and intraocular surgery; as well as in patients with pneumothorax or pulmonary hypertension as it rapidly increases pressure/volume ratio in a closed space.
- Fentanyl preferred in these instances

Neuromuscular blockers

	Mechanism	Notes
Succinylcholine	Depolarizing	Blocks Acetylcholine at endplate and binds to extra-junctional receptors, leading to desensitization of receptor and block of Na^+ channels; No effect on smooth muscle or cardiac function; May lead to hyperkalemia; allergic reactions noted; fasciculations noted with use (DO NOT USE IN PATIENTS WITH MUSCULAR DYSTROPHY)
Ruroconium	Non-depolarizing	Aminosteroid; Competes with acetylcholine at the nicotinic pre-synaptic receptor and at the end-plate by binding to at least one of the two α-subunits of the post-synaptic receptor; Does not counteract bradycardia induced by vagal stimulation; t½ 90 minutes; enhanced by isoflurane

Neuromuscular blockers

	Mechanism	Notes
Atracurium	Non-depolarizing	Benzylisoquilinium; Competes with acetylcholine at the nicotinic pre-synaptic receptor and at the end-plate by binding to at least one of the two α-subunits of the post-synaptic receptor; Histamine reaction; Malignant hyperthermia unlikely as effect not related to pseudocholinesterase level nor the absence of renal function; t½ 20 minutes; Enhanced by isoflurane; Cleared by ester hydrolysis and Hoffman elimination (major alkene product of asymmetrical amine becomes the least substituted and least stable)
Ganticurium	Non-depolarizing	Chlorofumirate diester

Neuromusclular blockers

- The effect of neuromuscular block is determined by peripheral nerve stimulation (Train of Four)
- Two electrodes are placed at the ulnar nerve and the medial abduction of the thumb is studied following electrical stimulus
- Alternatively, the tibial nerve may be employed
- If 3 of 4 stimuli lead to twitches, 75% of receptors engaged
- 2 of 4, 80%
- 1 of 4, 90%; safe to intubate
- 0 of 4, 100%

Neuromusclular blockers

- If too much blockade, 10% of patients will suffer residual weakness
- The reaction fades with repeated response to high frequency stimulation if a non-depolarizing agent

Neuromusclular block reversal

- Neostigmine
- Not if deep anesthesia
- Not if depolarizing agent employed
- Not repeatable as maximum blockade of acetylcholinesterase occurs with one dose
- 20 minute onset
- With the anti-muscarinic drug, glycopyrrolate, may be employed for reversal of atracurium

Neuromusclular block reversal

- Sugammadex
- Gamma-cyclodextrin
- Good for deep anesthesia
- Not if depolarizing agent employed
- Too small a dose leads to recurrent block; must evaluate response with peripheral nerve stimulation
- Clinically insignificant elevations of INR and APTT

Neuromusclular block reversal

- Cyclodextrins are hydrophilic on the outer surface because of tails of negatively charged hydroxyl groups; lipophilic on the inner surface.
- Lipophilic substances are encapsulated into the toroid formed by cyclodextrin, where they are tightly held as a result of a combination of van der Waals forces and charge transfer.
- Clyclodextrin encapsulates rorocuronium, diminishing plasma concentration, setting up muscle to plasma gradient
- Cleared by liver and kidney

Neuromusclular block reversal

- L-cysteine
- For benzylisoquilinium chlorofumarate diester blocker
- Cysteine replaces choline in ganticurium, leading to adduct formation of the fumarate double bond
- Non enzymatic breakdown (Hoffman elimination)
- Metabolite is hepatotoxic

Neuromusclular block reversal

- Calabadion
- Acyclic member of cucurbit[n]uril family of molecular containers
- Much larger cavity than sugammadex
- May also clear succinylcholine
- Reverses any depth of neuromuscular block (or agent)
- Reverses general anesthetic induction with ketamine or etomidate, but not propofol