General Anesthesia – Intravenous Anesthesia – Muscle relaxant for Medical Students

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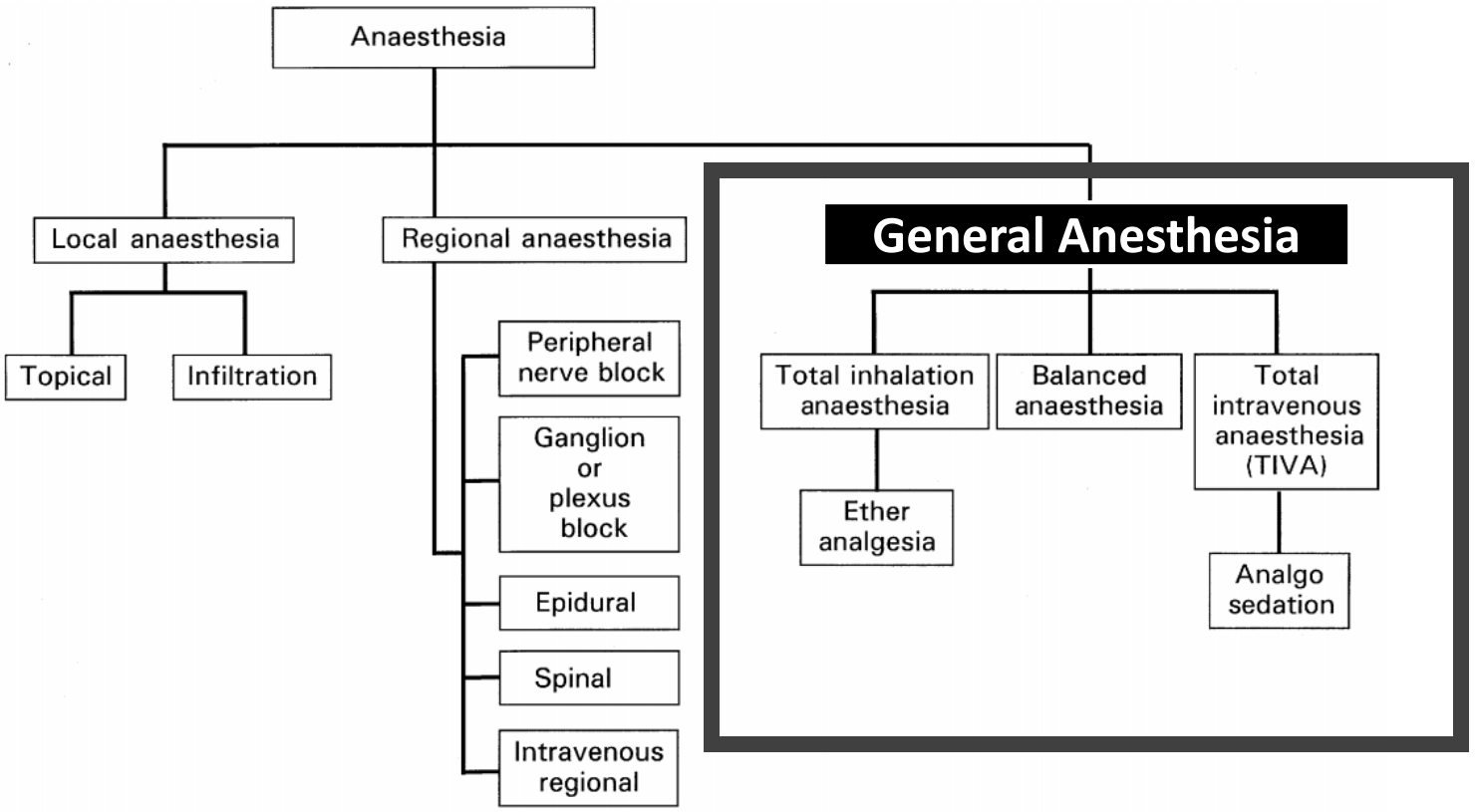
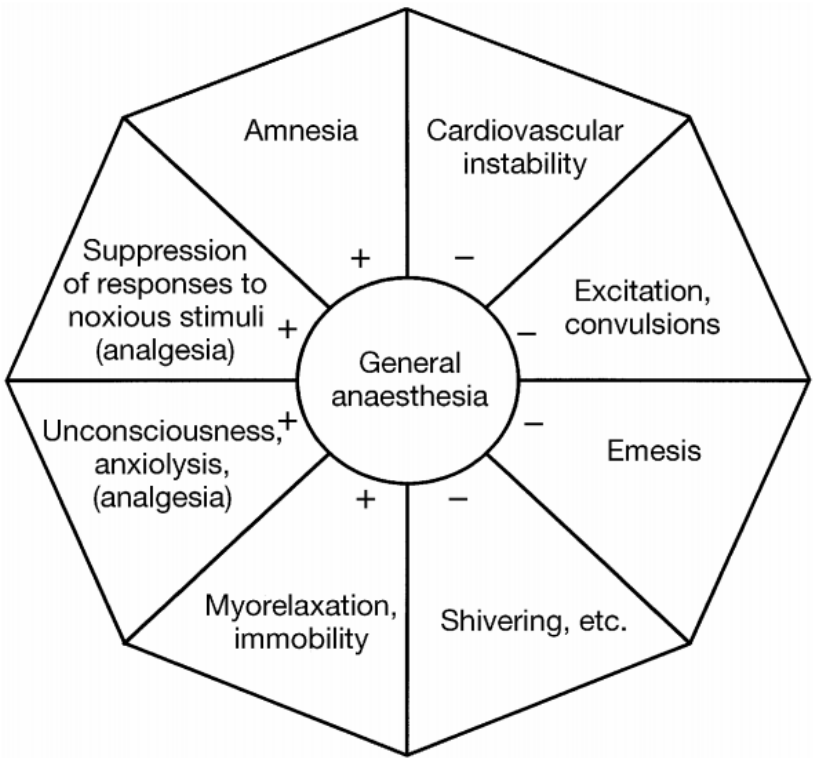
Types of Anaesthetic Procedures



B. W. Urban, and M. Bleckwenn. Br. J. Anaseth. 2002; 89:3-16.

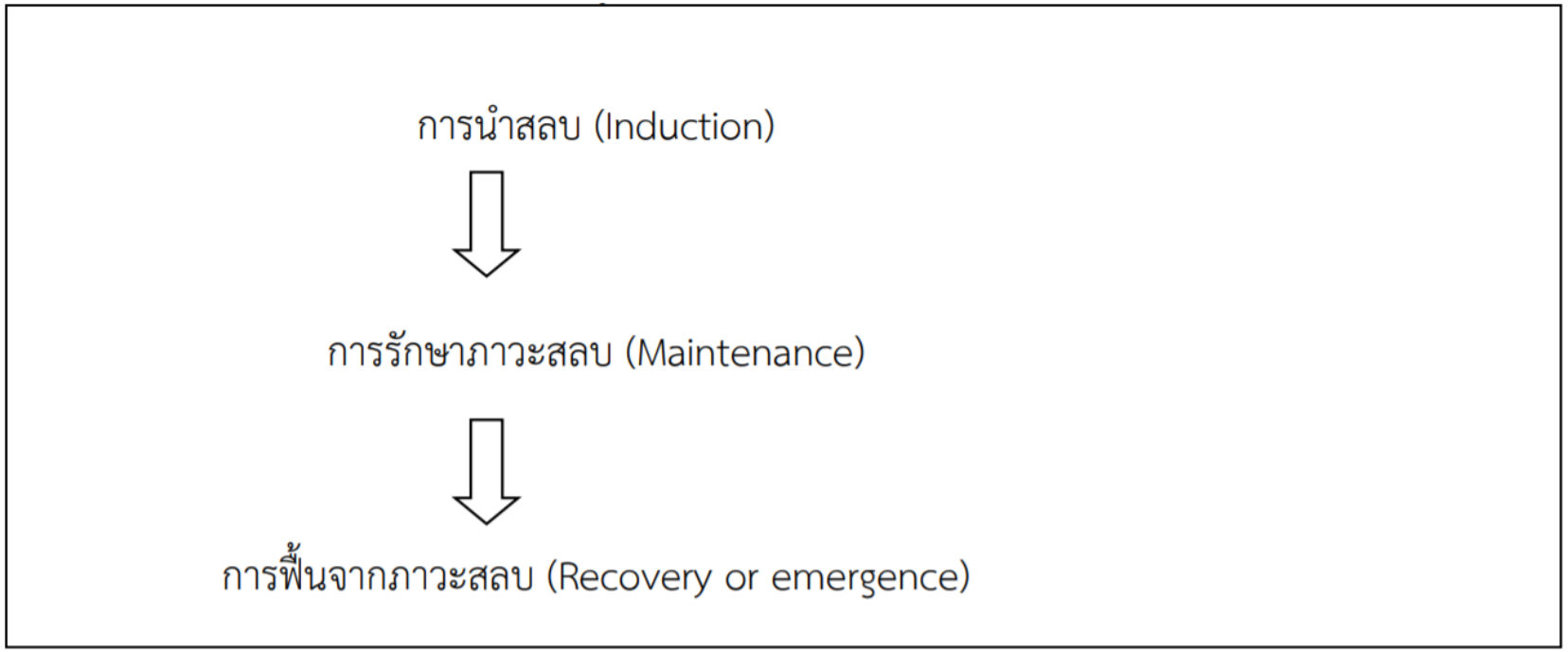
Components of General Anesthesia



- Analgesia
- Unconsciousness
- Muscle relaxation
- Amnesia

B. W. Urban, and M. Bleckwenn. Br. J. Anaseth. 2002; 89:3-16.

Establishment General Anesthesia



Pat Sullivan. Anesthesia for medical students. 1999.

Anesthetic-Surgical Balance

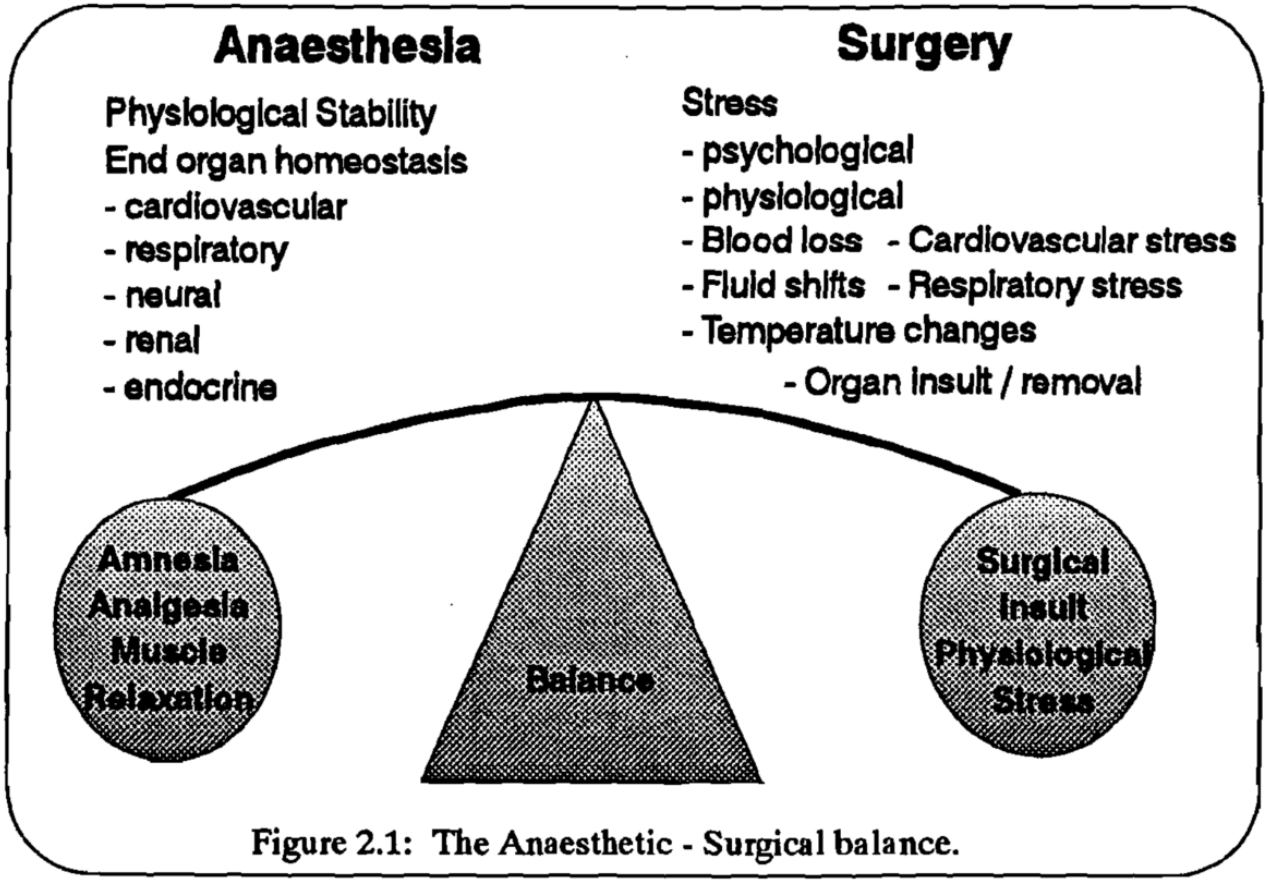


Figure 2.1: The Anaesthetic - Surgical balance.

Pat Sullivan. Anesthesia for medical students. 1999.

Intravenous Anesthetic Agents

Propofol

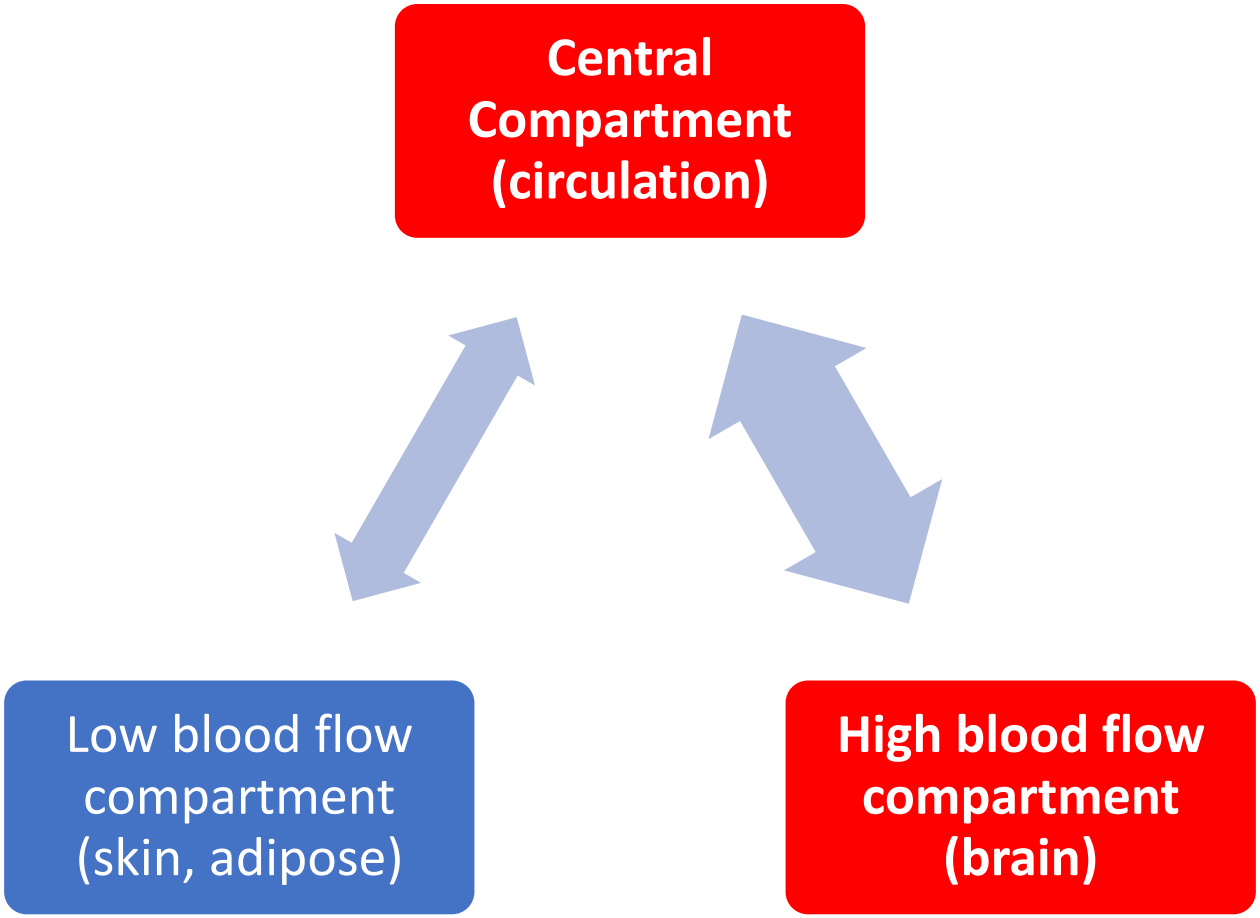
Etomidate

Thiopental

Ketamine

Benzodiazepine

Termination of Drug Effect Redistribution



Mechanism of Action

- Most IV anesthetics exert sedative and hypnotic effects via interaction with GABA receptors
  - GABA is primary inhibitory neurotransmitter in CNS
  - Activation of receptor causes increased chloride conductance, and therefore hyperpolarization (promotion of inhibition)
  - Other IV anesthetics exert effect via NMDA receptors (ketamine) or alpha-2 receptors (dexmedetomidine)
- Propofol and Barbiturates decrease the rate of dissociation of GABA and its receptor
- Benzodiazepines increase the efficiency of GABA-receptor and chloride ion channel coupling

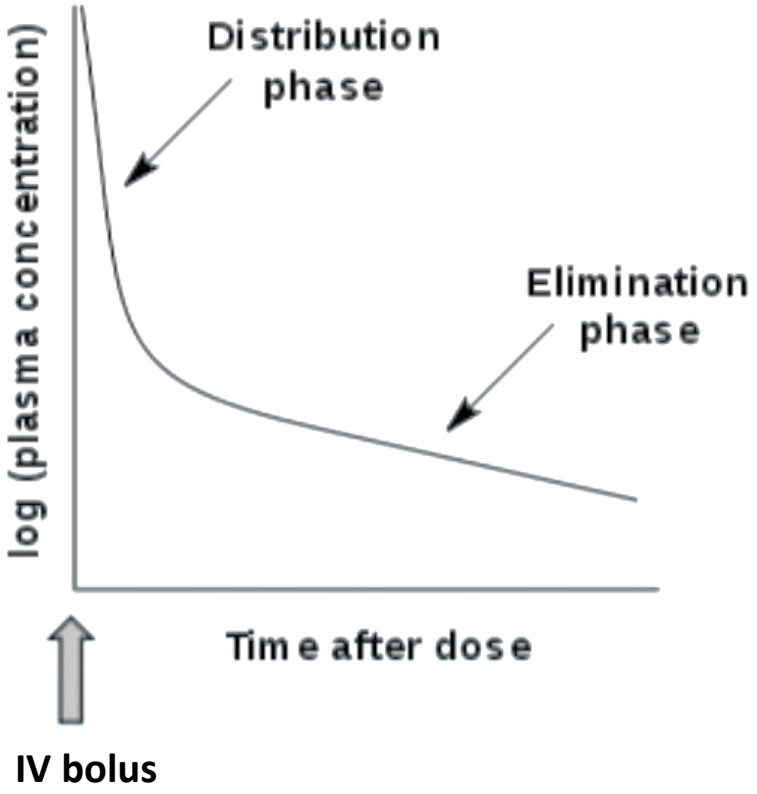
Propofol

- An akylphenol with hypnotic properties
- Produced in egg lecithin emulsion (egg yolk--not egg white--which is relevant to patient allergies, which is typically to egg white protein) because of high lipid solubility
  - Essentially insoluble in aqueous solutions
  - Formulations support growth of bacteria, good sterile technique and labeling of expiration times (typically 12 hours) is critical
- Pain on injection occurs in 32-67% of subjects; attenuated with IV lidocaine or administering drug in larger vein
- Infusion doses ~100-200 mcg/kg/min for hypnosis and ~25-75 mcg/kg/min for sedation (depends on desired level of consciousness and infusion duration)

Propofol Pharmacokinetics

- Hepatic metabolism (and lungs)
- Renal excretion

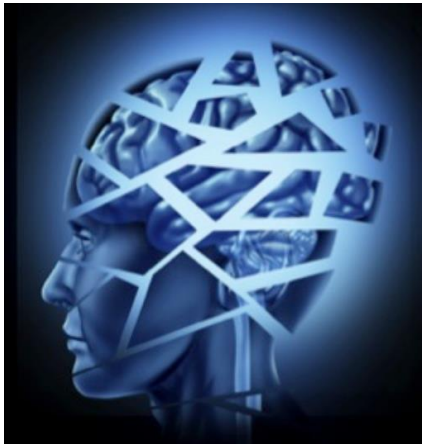
Induction Dose (mg/kg)	**1-2.5**
Duration of Action (min)	**3-8**
T ½ Distribution (min)	**2-4**
T ½ Elimination (min)	**4-23**
Clearance (ml/kg/min)	**20-30**
Protein Binding (%)	**97**
Volume of Distribution (L/kg)	**2-10**



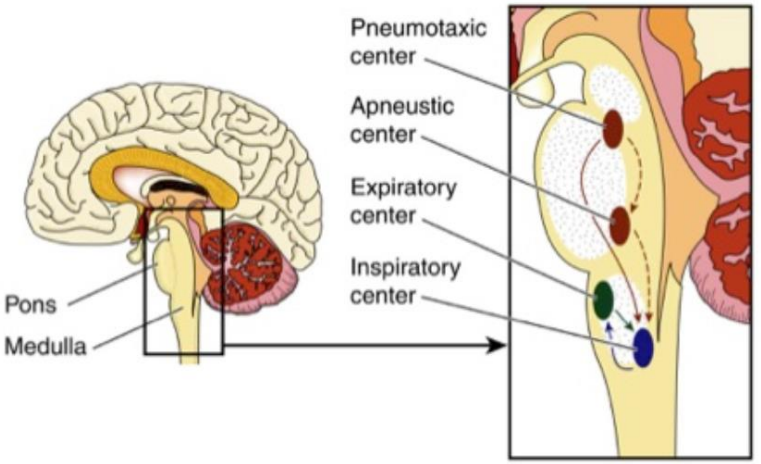
Imgae : Boghog CC license Wikimedia Commons

Propofol Pharmacodynamics

- CNS
  - Mediated through $GABA_A$
  - Hypnotic
  - NO analgesia
  - ↓CMR, CBF, ICP



- Respiratory System
  - ↓ TV > RR
  - ↓ response to hypoxia
  - ↓ response hypercapnia
  - Dose-dependent respiratory depression



Propofol Pharmacodynamics

- CVS
  - Why does propofol decrese BP on induction?

Venodilatation	**+++**
Arterial dilation	+
Decreased sympathetic outflow (and reflex inhibition)	++
Direct myocardial depression	+

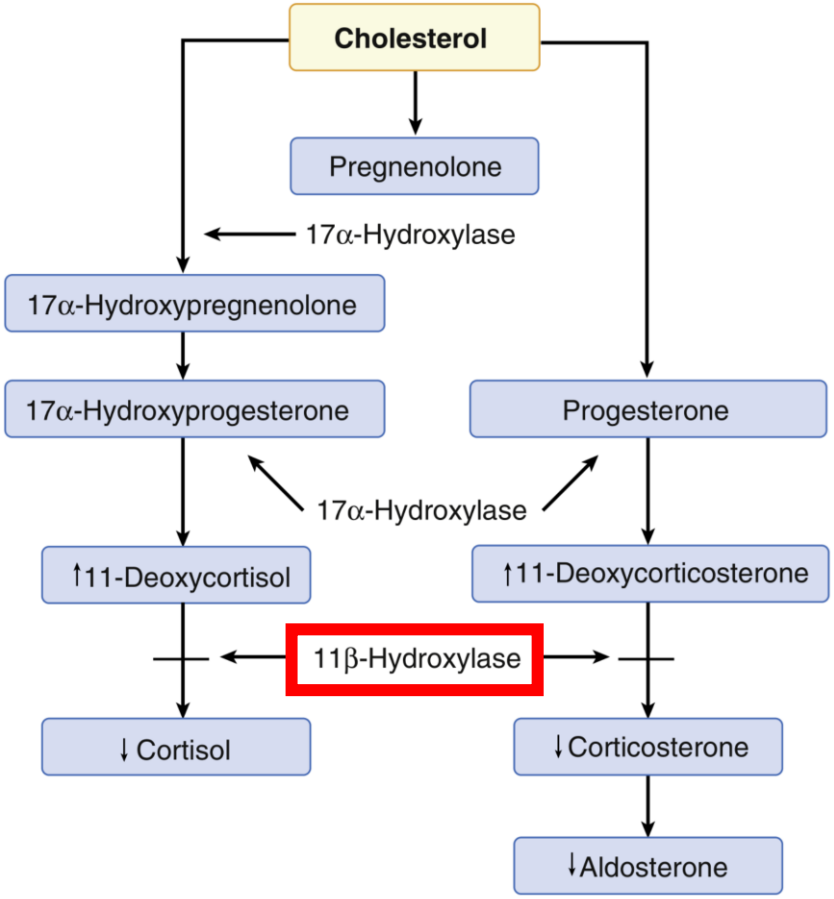
Ebert T. Sympathetic and hemodynamic efforts of moderate and deep sedation with propofol in humans. Anesthesiology. 2005;103:20-24.

Propofol

- Has anti-emetic properties – often used for TIVA cases and as background infusion for patients with PONV
- Propofol infusion syndrome (PRIS)
  - Risk in critically ill patients receiving high dose propofol infusions (>4mg/kg/hr) for prolonged periods of time.
  - Causes severe metabolic acidosis, rhabdomyolysis, cardiac failure, renal failure, hypertriglyceridemia, with high mortality, especially in children; treatment is supportive.

Etomidate

- Carboxylated imidazole derivative
- Hypnotic
- Water insoluble
- High incidence of pain on injection
- Impair cortisol production
- Inhibits adrenocortical synthetic function (11-beta-hydroxylase)
  - Inhibition for 4-8 hours even after a single induction dose; more prominent with infusions
- Myoclonus, hiccups, thrombophlebitis



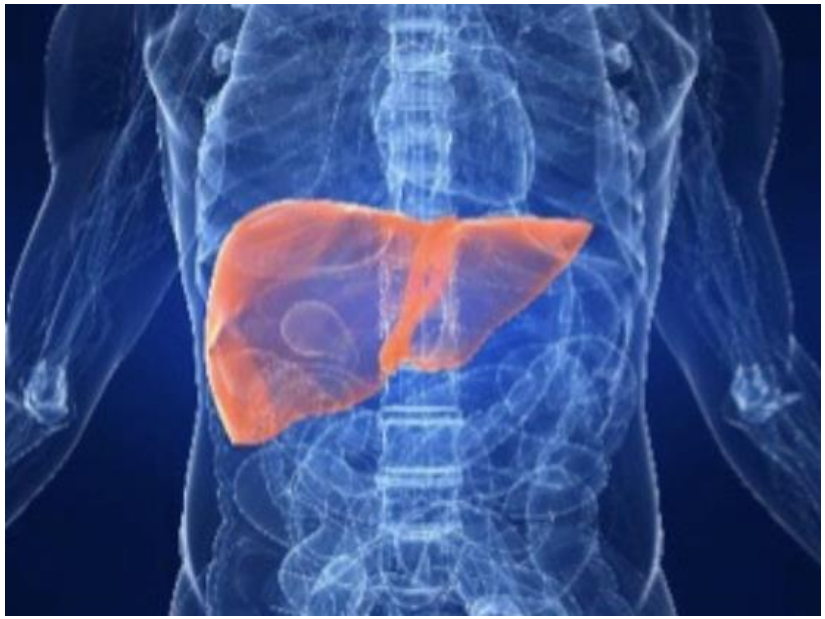
Miller, R. D. (2015). Miller's anesthesia (8th ed.). Philadelphia, PA:Elsevierj Churchill Livingstone.

Etomidate Pharmacokinetics

Induction Dose (mg/kg)	**0.2-0.3**
Duration of Action (min)	**3-8**
T ½ Distribution (min)	**2-4**
T ½ Elimination (min)	**2.9-5.3**
Clearance (ml/kg/min)	**18-25**
Protein Binding (%)	**77**
Volume of Distribution (L/kg)	**2.5-4.5**

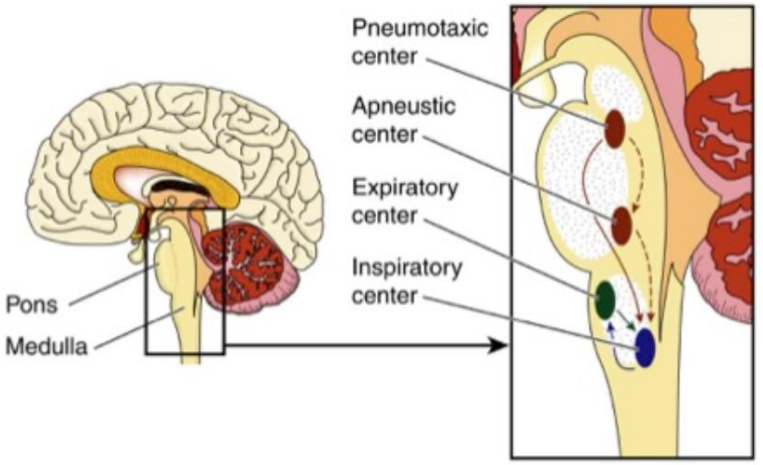
- Rapid onset due to high lipid solubility and large non-ionized fraction at physiologic pH

- Ester hydrolysis
- Duration of action linearly related to dose



Etomidate Pharmacodynamics

- CNS
  - ↓CMR, CBF, ICP
  - CPP maintained because less ↓ SBP
- CVS
  - Maintain hemodynamic stability (even in the presence of pre-existing disease)
    - Not induce histamine release
- Respiratory System
  - Less depression of respiratory center



Barbiturates : Thiopental

- Highly alkaline (pH 9)
- CAUTION
  - Can precipitate in acidic solutions (DO NOT MIX with Rocuronium or LR)
  - Intra-arterial injection
    - Can cause intense vasoconstriction, thrombosis and tissue necrosis; treat with papaverine and lidocaine or regional anesthesia-induced sympathectomy and heparinization
  - Hepatic and renal disease
  - Patient with acute intermittent porphyria

Thiopental Pharmacokinetics

Induction Dose (mg/kg)	**3-5**
Duration of Action (min)	**5-10**
T ½ Distribution (min)	**2-4**
T ½ Elimination (min)	**11**
Clearance (ml/kg/min)	**3.4**
Protein Binding (%)	**83**
Volume of Distribution (L/kg)	**1.5-3**

- Hepatic metabolism
- Rapidly redistributed into peripheral compartments
- Larger doses can saturate peripheral compartments
  - prolonged duration of action

Thiopental Pharmacodynamics

- CNS
  - GABA agonist
  - Potent cerebral vasoconstrictor
  - ↓CMR, CBF, ICP
- CVS
  - ↓ sympathetic outflow
  - Peripheral vasodilatation
  - ↓ SVR, direct myocardial depressant
  - Modest ↓ BP
  - Exaggerated hemodynamic effects in unstable patients
- Respiratory System
  - Dose-dependent respiratory depression
  - Sympathetic stimulation
  - Bronchodilatation
  - Causes salivation

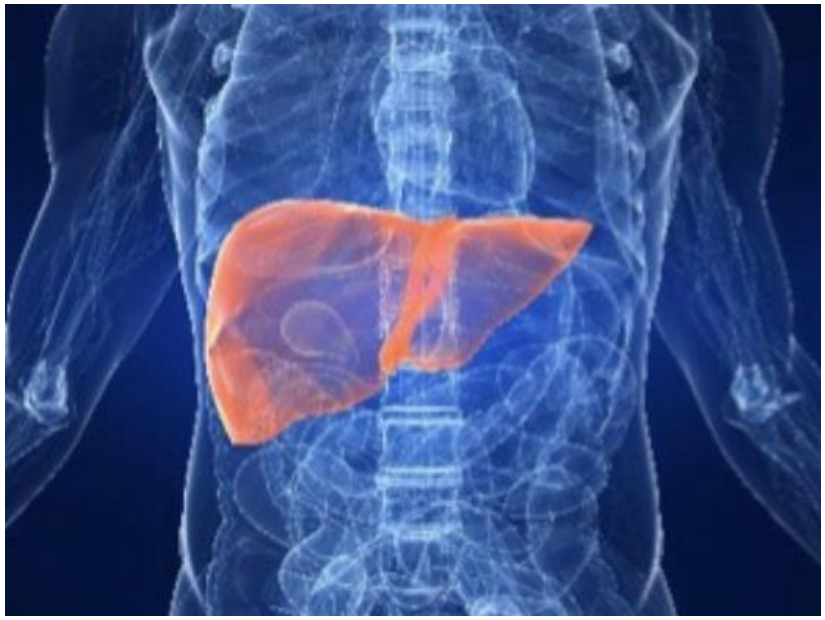
Ketamine

- Phencyclidine derivative
- Significant analgesia
- Produces a dissociative anesthetic state
  - Profound analgesia and amnesia despite maintenance of consciousness
  - High incidence of psychomimetic reactions (attenuated by co-administration of midazolam)
- Highly lipid soluble
- Useful for chronic pain patients (common dose for intra-operative management is 0.5-1 mg/kg prior to incision (after intubation, unless using for induction) and then 0.25 mg/kg each hour (infusion or bolus)

Ketamine Pharmacokinetics

Induction Dose (mg/kg)	**1-2**
Duration of Action (min)	**5-10**
T ½ Distribution (min)	**11-16**
T ½ Elimination (min)	**2-4**
Clearance (ml/kg/min)	**12-17**
Protein Binding (%)	**12**
Volume of Distribution (L/kg)	**3.1**

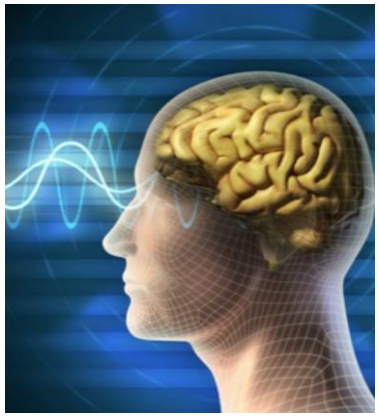
- Metabolized in liver by P450
- Metabolite is active
- Hepatic disease prolongs effects



Peltoniemi MA, et al. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. Clin Pharmacokinet. 2016;55(9):1059-1077.

Ketamine Pharmacodynamics

- CNS
  - ↑CMR, CBF, ICP
  - NMDA antagonist (implications in chronic pain)
  - Vivid dreams or hallucination (10-30%)



- Respiratory System
  - Minimal respiratory depression
  - Most likely to preserve airway reflexes among the IV anesthetics

Ketamine Pharmacodynamics

- CVS
  - Preserves HR, CO, MAP via sympathetic stimulation
  - Cardio-stimulating effects secondary to direct sympathetic stimulation
    - Can be unmasked in patients with increased sympathetic outflow
    - Negatively effects myocardial oxygen supply-demand ratio
  - Intrinsic myocardial depressant, may be significant in severely ill patients with depleted catecholamine reserves

Benzodiazepines

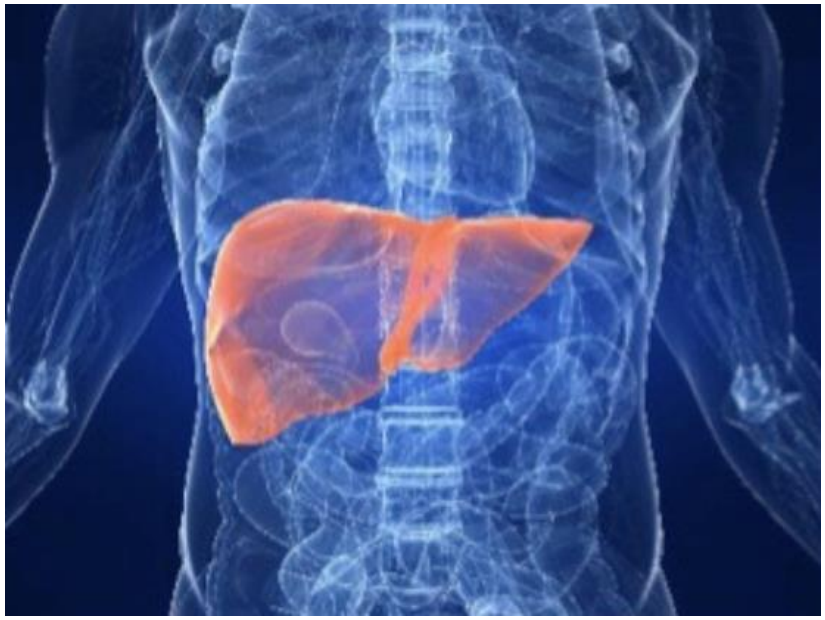
- Highly lipophilic
- Anxiolytic, amnestic, sedative, hypnotic, anticonvulsant properties (but not analgesia!)
- Midazolam, Diazepam, Lorazepam
- Flumazenil = specific antagonist
  - Very short acting
  - 45-90 minutes of action following 1-3 mg dose
    - May see re-sedation as benzodiazepine is eliminated more slowly compared to effects of flumazenil

Olkkoia KT, Ahonene J. Midazolam and other benzodiazepines. Handb Exp Pharmacol. 2008;182:335-60.

Midazolam Pharmacokinetics

Induction Dose (mg/kg)	**0.05-0.15**
Duration of Action (min)	**15-20**
T ½ Distribution (min)	**7-15**
T ½ Elimination (min)	**1.7-2.6**
Clearance (ml/kg/min)	**6.4-11**
Protein Binding (%)	**94**
Volume of Distribution (L/kg)	**1.1-1.7**

- Metabolized in liver
- Midazolam – ok for infusion



- Premedication dose 0.04-0.08 mg/kg IV
- Induction dose 0.1-0.2 mg/kg IV

Miller, R. D. (2015). Miller's anesthesia (8th ed.). Philadelphia, PA:Elsevierj Churchill Livingstone.

Benzodiazepine Pharmacodynamics

- CNS
  - ↓CMR, CBF
    - Smaller effect than propofol
  - GABA agonist
- CVS
  - Midazolam > diazepam
  - ↓ SVR and BP when used as induction dose
  - HR and CO relatively unchanged
- Respiratory System
  - Dose dependent respiratory depression
  - Most likely to preserve airway reflexes among the IV anesthetics
  - Increases PVR
  - Sympathetic stimulation
    - Bronchodilatation
    - Causes salivation

IV Anesthetic Agent

Induction Characteristics and Dosage Requirements for the Currently Available Sedative–Hypnotic Drugs

DRUG NAME	INDUCTION DOSE (mg/kg)	ONSET (sec)	DURATION (min)	EXCITATORY ACTIVITY*	PAIN ON INJECTION*	HEART RATE†	BLOOD PRESSURE†
Thiopental	3–6	<30	5–10	+	0–+	↑	↓
Methohexital	1–3	<30	5–10	++	+	↑↑	↓
Propofol	1.5–2.5	15–45	5–10	+	++	0–↓	↓↓
Midazolam	0.2–0.4	30–90	10–30	0	0	0	0/↓
Diazepam	0.3–0.6	45–90	15–30	0	+/+++	0	0/↓
Lorazepam	0.03–0.06	60–120	60–120	0	++	0	0/↓
Etomidate	0.2–0.3	15–45	3–12	+++	+++	0	0
Ketamine	1–2	45–60	10–20	+	0	↑↑	↑↑

*0 = none; + = minimal; ++ = moderate; +++ = severe.

†↓ = decrease; ↑ = increase.

Clinical Anesthesia 8th; Barash, P.; Lippincott Williams and Wilkins; 2017.

IV Anesthetic Agent

Pharmacokinetic Values for the Currently Available Intravenous Sedative–Hypnotic Drugs

DRUG NAME	DISTRIBUTION HALF-LIFE (min)	PROTEIN BINDING (%)	DISTRIBUTION VOLUME AT STEADY STATE (L/kg)	CLEARANCE (mL/kg/min)	ELIMINATION HALF-LIFE (h)
Thiopental	2–4	85	2.5	3.4	11
Methohexital	5–6	85	2.2	11	4
Propofol	2–4	98	2–10	20–30	4–23
Midazolam	7–15	94	1.1–1.7	6.4–11	1.7–2.6
Diazepam	10–15	98	0.7–1.7	0.2–0.5	20–50
Lorazepam	3–10	98	0.8–1.3	0.8–1.8	11–22
Etomidate	2–4	75	2.5–4.5	18–25	2.9–5.3
Ketamine	11–16	12	2.5–3.5	12–17	2–4

Clinical Anesthesia 8th; Barash, P.; Lippincott Williams and Wilkins; 2017.

Pharmacodynamics

Drug	Induction Dose (mg/kg)	Effects	Pearls
Propofol	1.5-2.5	**Neuro:** Decreases cerebral metabolic O2 requirements, cerebral blood flow, intracranial pressure **CV**: Decreases SVR, direct myocardial depressant **Pulm:** Dose-dependent respiratory depression (apnea in 25-35% of patients)	-Pain on injection (32-67%) -can be attenuated with lidocaine and with injection into larger veins -Antiemetic properties -Anticonvulsant properties
Etomidate	0.2-0.3	**Neuro:** Decreases CMRO2, CBF, ICP **CV**: Maintains hemodynamic stability (minimal cardiac depression) **Pulm:** Minimal respiratory depression (no histamine release)	-Pain on injection -High incidence of PONV -Myoclonus -Inhibits adrenocortical axis
Thiopental	3-5	**Neuro:** Decreases CMRO2, CBF, ICP **CV**: Decreases SVR, direct myocardial depressant **Pulm:** Dose-dependent respiratory depression	-Anticonvulsant properties -Can precipitate when injected with acidic fluids (i.e LR)
Ketamine	1-2	**Neuro:** Increases CMRO2, CBF, ICP **CV**: Cardio-stimulating effects (negatively effects myocardial supply-demand) **Pulm:** Minimal respiratory depression; bronchodilation; most likely of all to protect airway reflexes	-Analgesic effects -Intrinsic myocardial depressant effects which may be unmasked with depleted catecholamines

References

- Clinical Anesthesia 8 th Edition; Barash P., Cullen B., Stoelting R.; Lippincott Williams and Wilkins; 2017.
- Clinical Anesthesiology 6 th edition; Morgan G.E., Mikhail M.S., Murray M.J.; Lange Medical Books/McGraw-Hill, 2018.
- Miller's Anesthesia 8 th edition; Miller R.; Churchill Livingstone, 2014.
- Avramov M. Anesth Analg 1995;81:596-602

Neuromuscular Blocking Agents

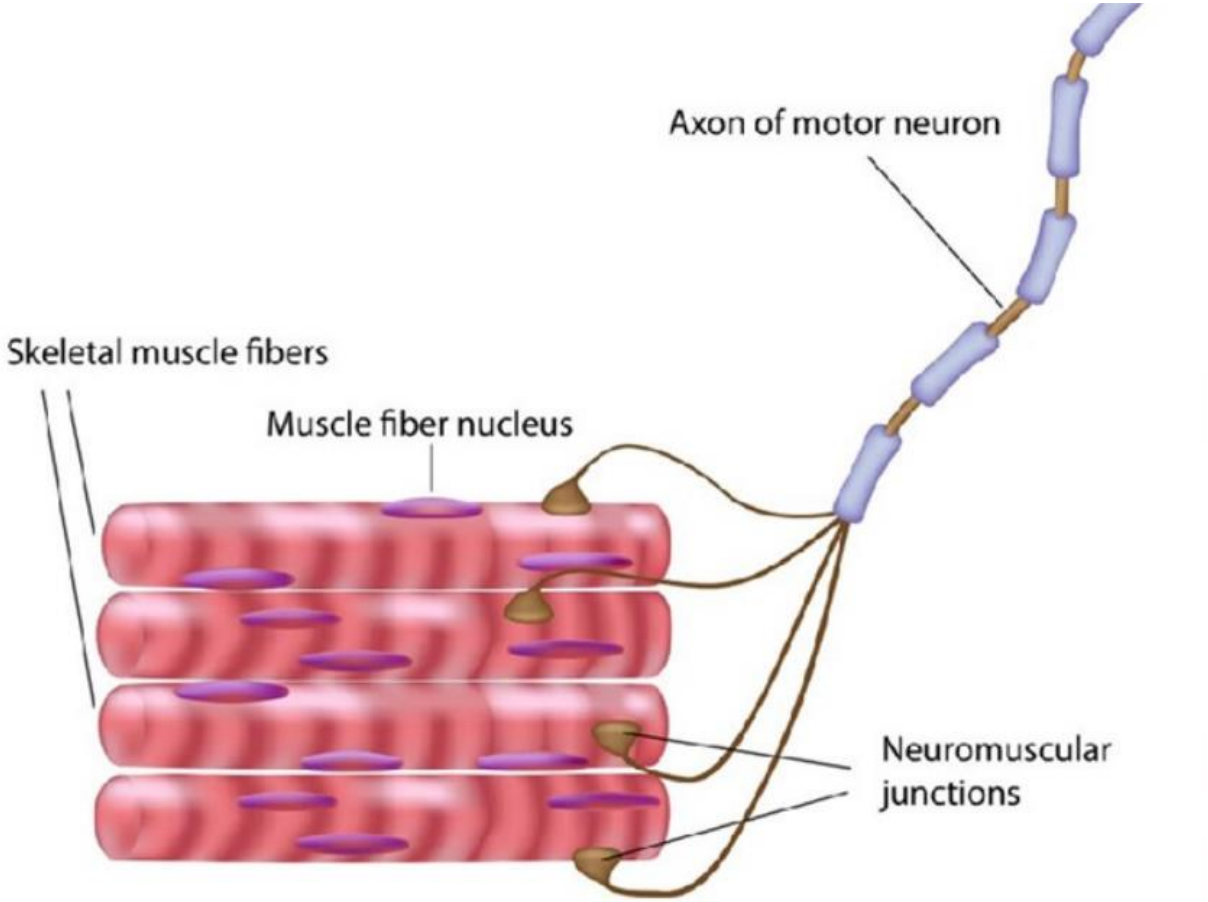
Neuromuscular Blocking Agents

- Agents that paralyzes the skeletal muscles through inhibition of motor nerve transmission at the neuromuscular junction
- Neuromuscular blocking agents may also be referred to as “paralytics”

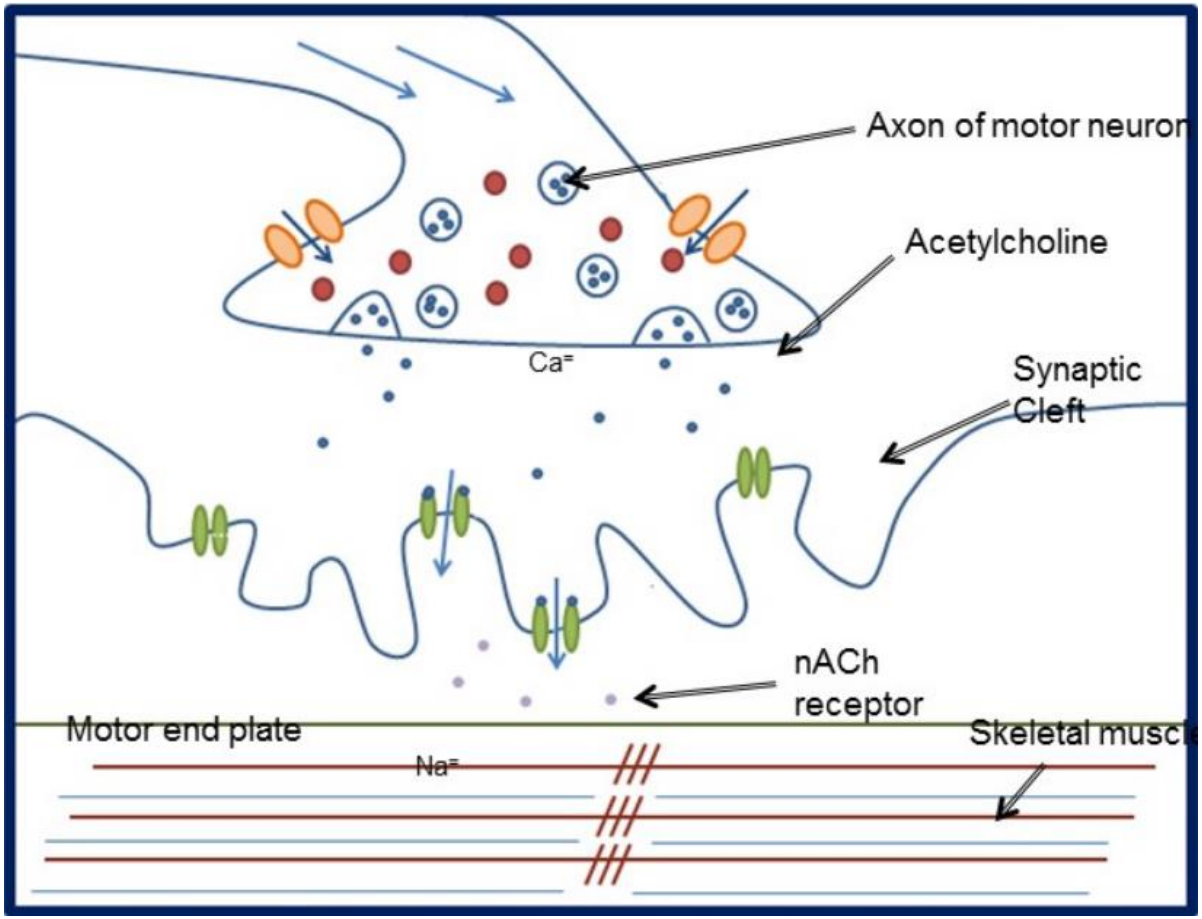
Role of NMBA in Clinical Practice

- Control muscle relaxation during surgery
- Emergency intubation
- Facilitate mechanical ventilation
- Decreaser intracranial pressure (ICP)
- Treat shivering from targeted temperature management

Innervation of Skeletal Muscle

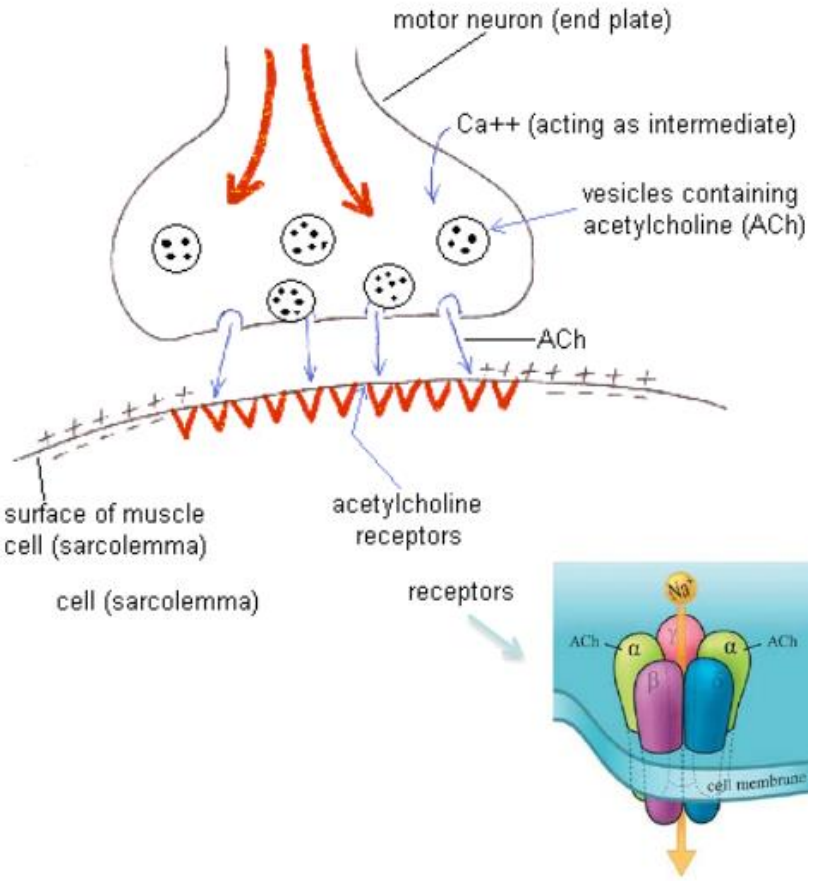


The Neuromuscular Jumction



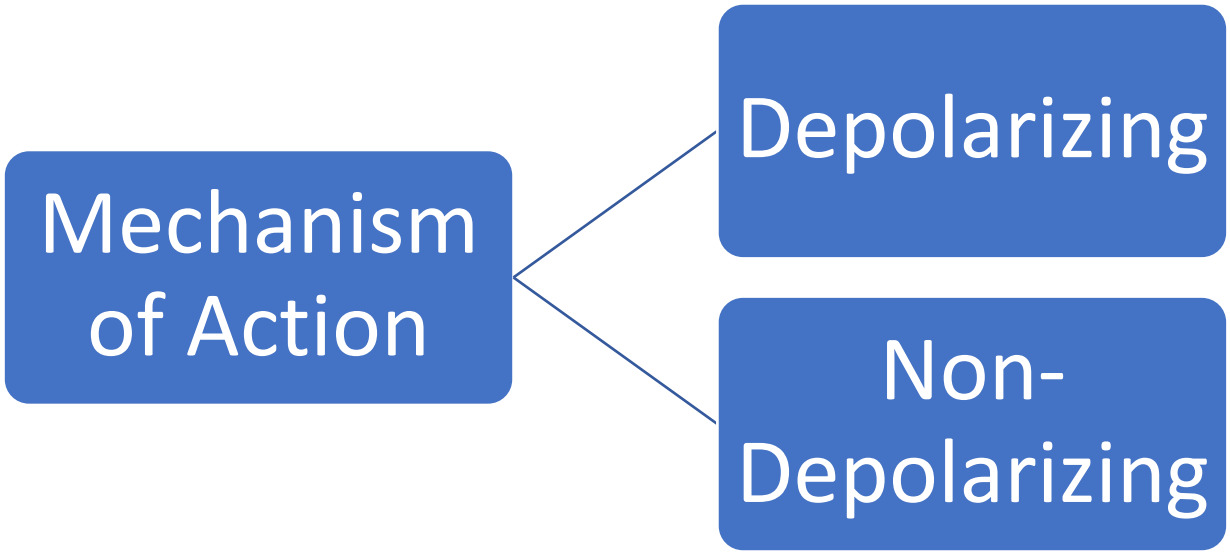
Neuromuscular Transmission

- Action potential depolarizes motor neurons Ca++ influx vesicles fuse and release Ach
- ACh across synaptic cleft and binds nicotinic receptors
- When ACh binds both αsubunits, receptor ion channel opens with ion movement of Na+ and Ca++ in, K+ out

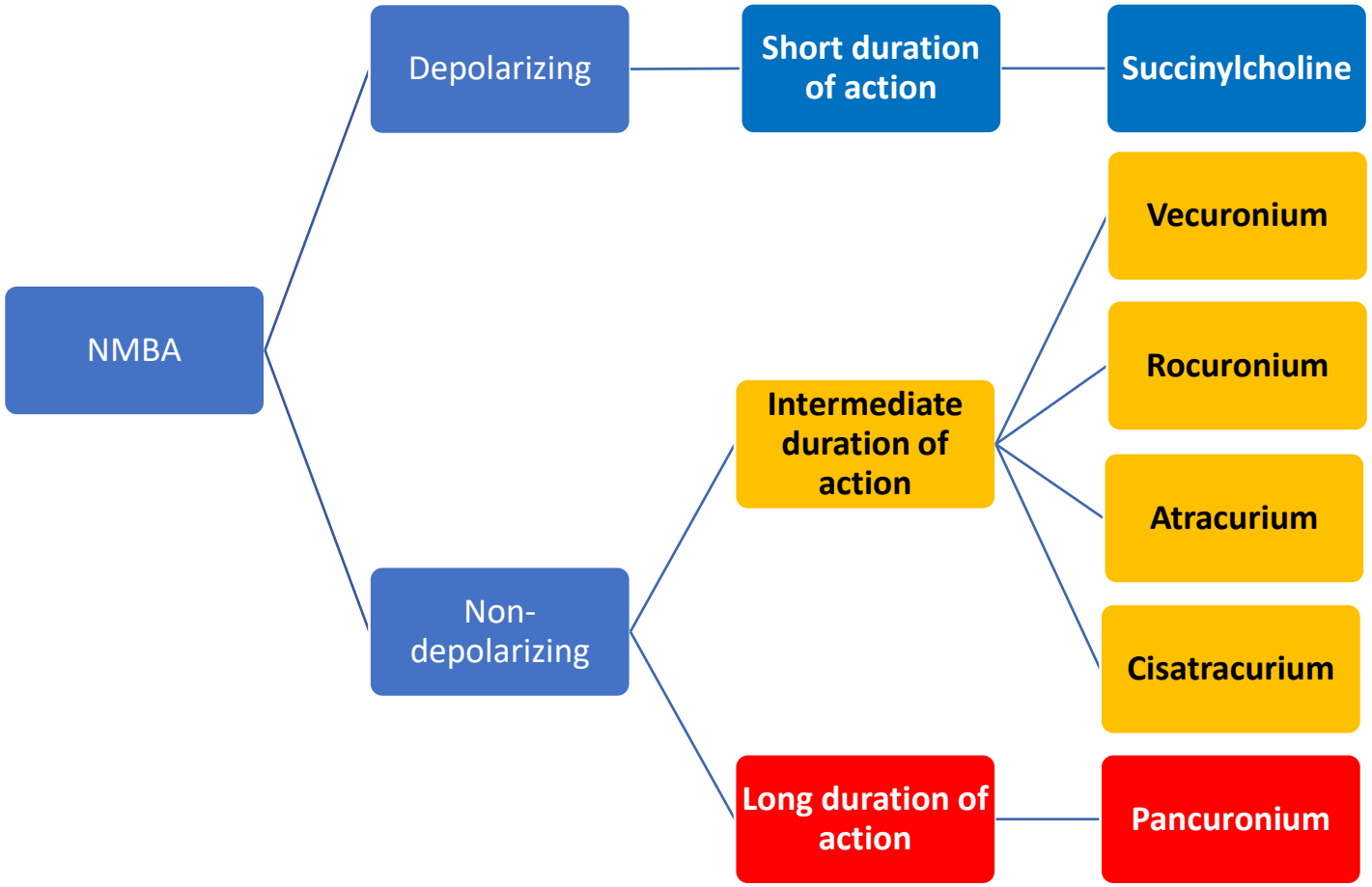


Mechanism of Action

- Classified based on their mechanism of Action:

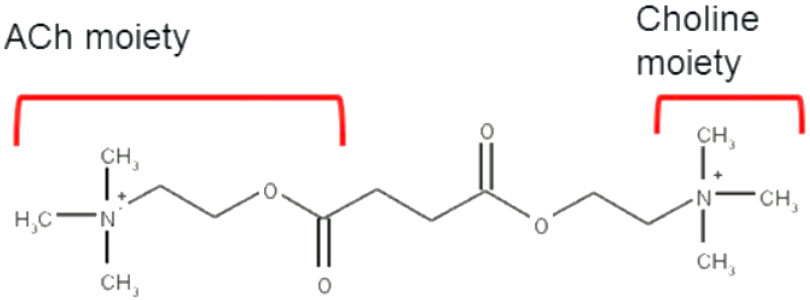


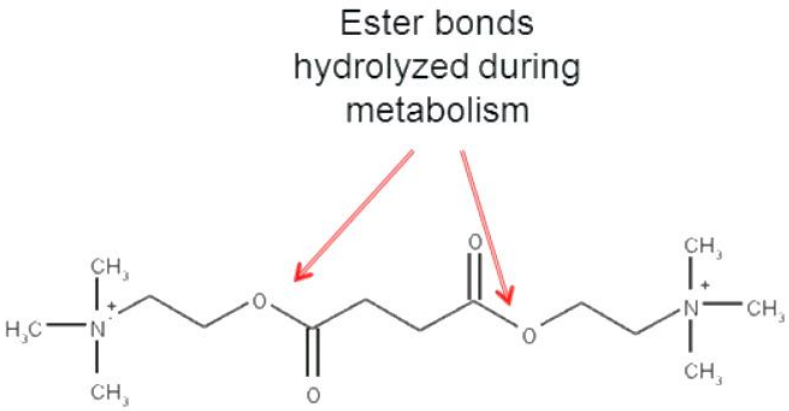
Neuromuscular Blocking Agents



Depolarizing NMBA: Mechanism of Action

- **Succinylcholine**
  - Analogue of Acetylcholine
    - Two ACh molecules joined by methyl groups
  - Agonizes nACh Receptor
- Hydrolysed by pseudocholinesterase (aka: plasma cholinesterase, butyrylcholinesterase)
- Not degraded by Acetylcholinesterase





Depolarizing NMBA: Mechanism of Action

- ACh receptor agonist and prolonged muscle depolarization
  - Competitive agonist at nACh receptor
  - Prevents ACh from binding at the nACh receptor
  - Prevents potentiation of action potentials and prevents muscle contractions

Depolarizing NMBA: Succinylcholine

- Intubating Dose: 1.5 mg/kg : preferred for RSI
  - Dose based on total body weight (TBW)
- **Rapid Onset**: within 45-60 sec
- **Short acting**: duration 6-10 min depending on dose
- Hydrolysed by pseudocholinesterase
- Enzymatic deficiency can lead to prolonged block
  - 1:3000 individuals are homozygous for an abnormal plasma cholinesterase; paralysis can last 3-8 hours.
- Should not be used for sustained neuromuscular blockade

Naguib M, Samarkandi AH, Emad El-Din M, et al. The dose of succinylcholine required for excellent endotracheal intubating conditions. Anesth Analg. 2006;105:151-5.
Lemmens HJ, Brodsky JB. The dose of succinylcholine in morbid obesity. Anesth Analg. 2006;102:438-42.

Adverse Effects

- Bradycardia : esp children - often given with atropine
- ↑ ICP & intraocular pressure
- ↑ intragastric pressure & LES pressure
- Myalgia : common in women and ambulatory patients
- Fasciculations
  - ↓ with defasciculating dose of rocuronium= 0.3 mg/kg 3 minutes prior to succinylcholine
- Anaphylaxis (approx. 1:5000 – 1:10,000)
- Malignant hyperthermia
- Hyperkalemia – mild to life threatening

Cunningham AJ, Barr P. Intraocular pressure-physiology and implications for anesthetic management. Can Anaesth Soc J. 1986; 33: 195-208.
Vachon CA, Warner DO, Bacon DR. Succinylcholine and the open globe: tracing the teaching. Anesthesiology. 2003;99:220-3.
Wappler F. Malignant hyperthermia. Eur J Anaesthesiol. 2001;18:632-52.
Wong SF, Chung F. Succinylchline-assoicated postoperative myalgia. Anaesthesia. 2000;55:144-152.

Hyperkalemia and Succinylcholine

- Induction dose typically ↑K 0.5-1.0 mEq/L
- May be life-threatening in at risk populations (↑ K 5-15 mEq/L → cardiac arrhythmia : death)
- Conditions with upregulated junctional and extrajunctional cholinergic receptors
  - Burn injury (after 24-48hrs)
  - Muscular dystrophy, myotonias, prolonged immobility
  - Crush injury
  - Upper motor neuron insults from stroke and tumors
  - Neuromuscular disorders

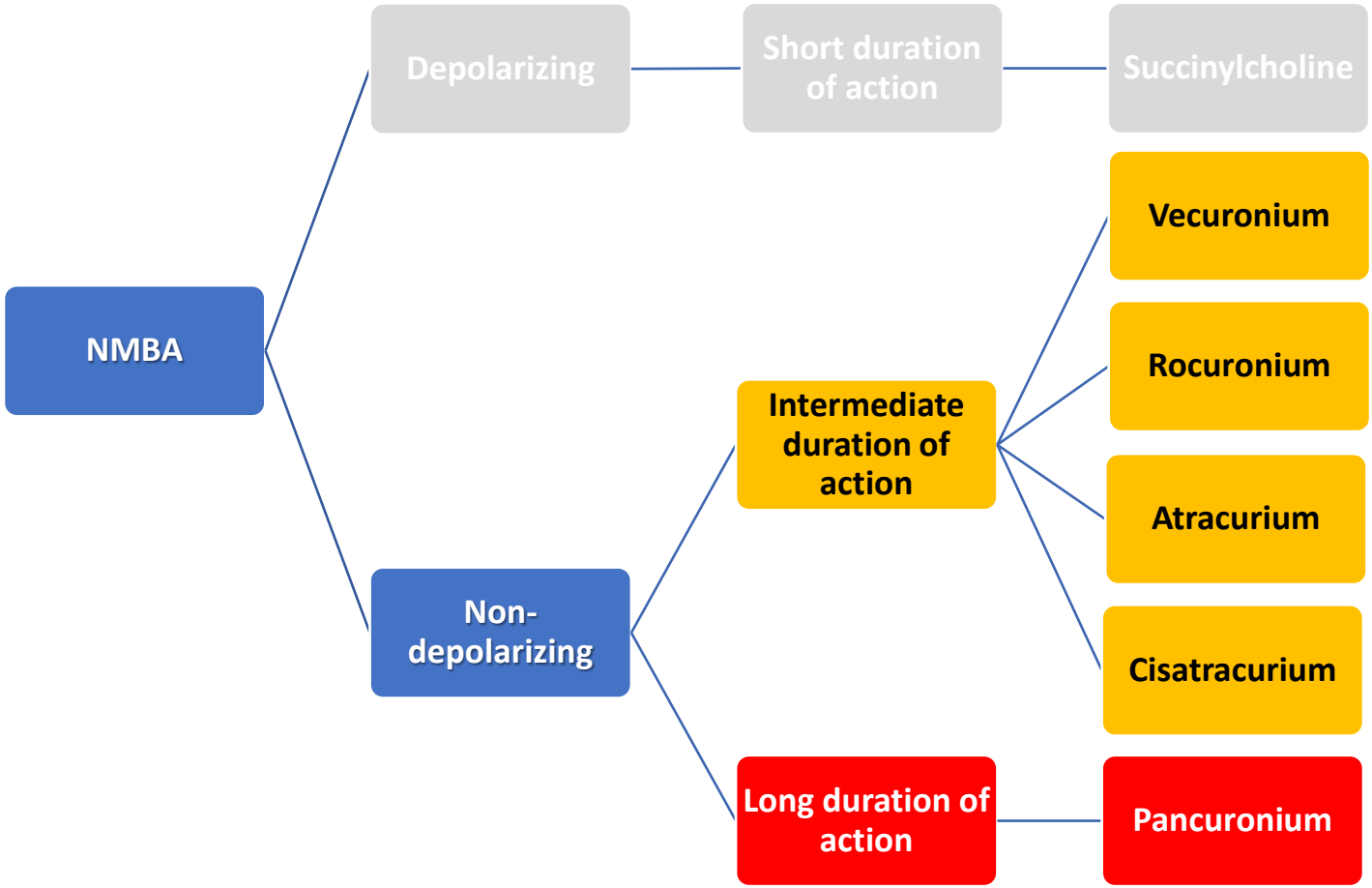
Contraindications to Sux

- Conditions with upregulated junctional and extrajunctional cholinergic receptors
- History malignant hyperthermia ± associated diseases.
- Open globe (anterior chamber): causes transient ↑ IOP
- Normo-kalemic renal failure is NOT a contraindication

Nondepolarizing NMBA

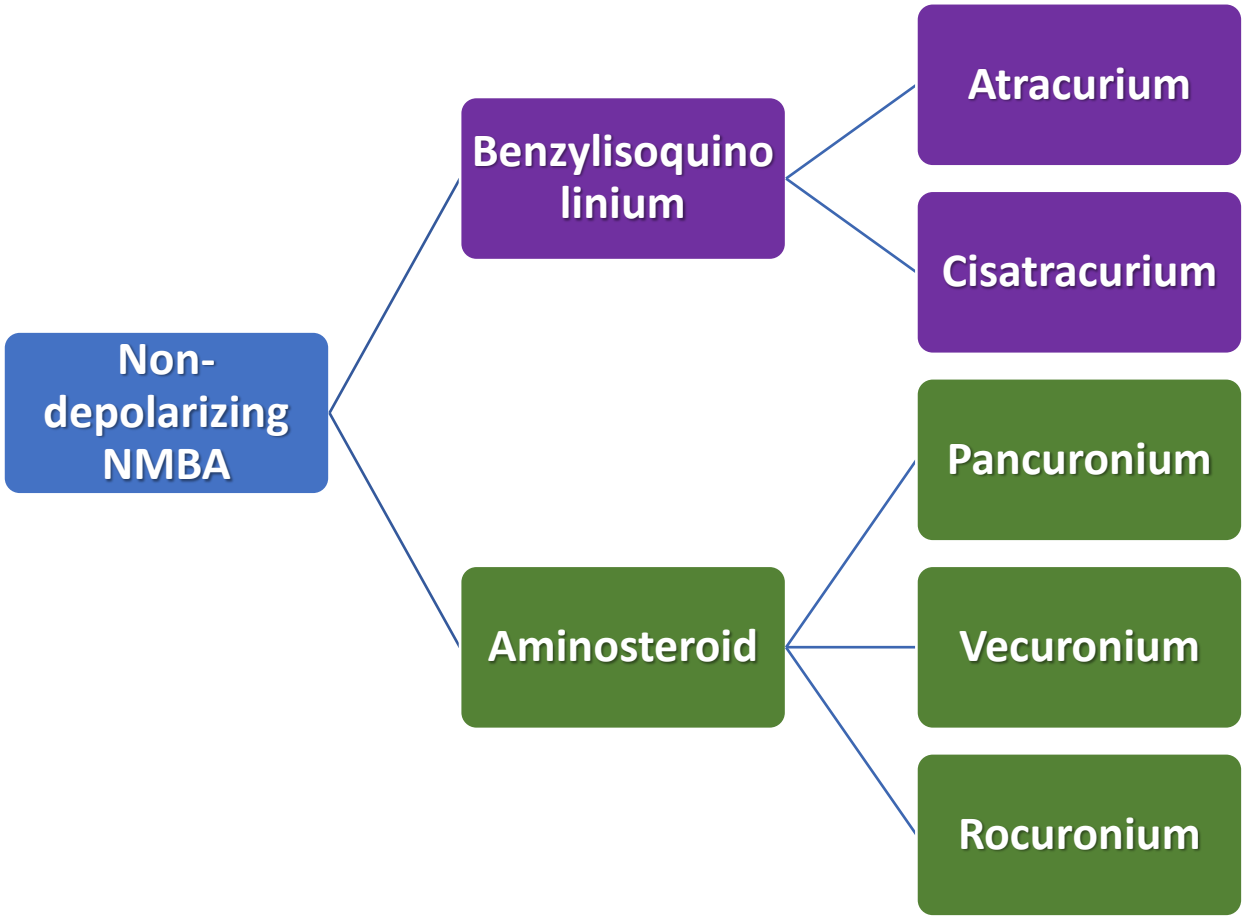
- Mechanism of action: competitive inhibition of nicotinic Ach receptor (nAChR) at the NMJ.
- The most used nondepolarizing agents are: rocuronium, cisatracurium, and atracurium

Neuromuscular Blocking Agents



Murrell MT, Savarese JJ. New vistas in neuromuscular blockers. In: Kaye AD, Kaye AM, Urman RD. editors. Essentials of pharmacology for anesthesia, pain medicine, and critical care. New York: Springer-Verlag;2015.

Structural Classification



Appiah-Ankam J, Hunter JM. Pharmacology of neuromuscular blocking drugs. Contin Educ Anaesth Crit Care Pain. 2004;4:2-7.

Nondepolarizing NMBA

- Adverse effects
  - Vagal blockade → tachycardia
  - Histamine release
- Drug-drug interactions
  - Effect potentiated by inhaled anesthetics
  - Drugs that induce hepatic enzymes (i.e. phenytoin)
- Drug-disease interactions
  - Hypothermia
  - Acidosis
  - Hypokalemia and hypocalcemia

Swen J, Rashkovsky OM, Ket JM, Koot HW, Hermans J, Agoston S. Interaction between nondepolarizing neuromuscular blocking agents and inhaled anesthetics. Anesth Analg. 1989;69:752-5.

Intermediate-Acting Non-Depolarizing NMBA

Intermediate-acting Rocuronium

- Intermediate-acting
  - Onset: <2 mins (90 S)
  - Duration: 35-75 mins
- Dose
  - Intubating: 0.6 mg/kg
  - **RSI: 1-1.2 mg/kg**
  - Continuous infusion: 10-12 mcg/kg/min
- Elimination
  - Prolonged in hepatic failure
  - No significant renal excretion
- Adverse Effects
  - Minimal vagal blockade
  - No histamine release

Intermediate-acting Vecuronium

- Intermediate-acting
  - Onset: 2-3 mins
  - Duration: 45-90 mins
- Dose
  - Intubating: 0.08-0.1 mg/kg
  - Continuous infusion: 8-12 mcg/kg/min
- Elimination
  - Prolonged in hepatic failure
  - Prolonged in renal failure
- Adverse Effects
  - Minimal vagal blockade
  - No histamine release

Intermediate-acting Atracurium

- Intermediate-acting
  - Onset: 2.5-3 mins
  - Duration: 30-45 mins
- Dose
  - Intubating: 0.4-0.5 mg/kg
  - Continuous infusion: 4-12 mcg/kg/min
- Elimination
  - No hepatic elimination
  - No renal excretion
  - **Dependent on Hoffman elimination and ester hydrolysis**
- Adverse Effects
  - No vagal blockade
  - Histamine release, particularly at high doses

Intermediate-acting Cisatracurium

- Intermediate-acting
  - Onset: 2-3 mins
  - Duration: 40-75 mins
- Dose
  - Intubating: 0.1-0.2 mg/kg
  - Continuous infusion: 2.5-3 mcg/kg/min
- Elimination
  - No hepatic elimination
  - No renal excretion
  - **Dependent on Hoffman elimination and ester hydrolysis**
- Adverse Effects
  - No vagal blockade
  - Minimal histamine release

Long-Acting Non-Depolarizing NMBA

Long-Acting Pancuronium

- Long-acting
  - Onset: 2-3 mins
  - Duration: 60-120 mins
- Dose
  - **Bolus/RSI: 0.06-0.1 mg/kg**
  - Continuous infusion: 1-2 mcg/kg/min
- Elimination
  - Prolonged in hepatic failure
  - Prolonged in renal failure
- Adverse Effects
  - Significant vagal blockade
  - No histamine release

Neuromuscular Blocking Agents

Agent	ED95 (mg/kg)	Intubating Dose (mg/kg)	Onset (min)	Duration to 25% recovery (min)	Intra-op Mainenance	Metabolism / Excretion
Succinylcholine	0.3	1	1-1.5 min	6-8 min	Rarely done	plasma cholin-esterase
Rocuronium	0.3	0.6	1.5-2	30-40	0.1 -0.2 mg/kg prn	>70% Liver
		RSI 1.2	1	>60		Bile + Urine
Vecuronium	0.05	0.1 -0.2	3-4	35-45	0.01 -0.02 mg/kg prn	50% Liver / Bile + Urine*
Cisatracurium	0.05	0.15-0.2	5-7	35-45	0.3 mg/kg q20min prn	Hoffman elimination

*Vecuronium's 3-OH metabolite (80% potency) accumulates in renal failure. Rocuronium however does not have any active metabolites

**Recovery of neuromuscular function takes place as plasma concentrations decline, and the greater part of this decrease initially occurs primarily because of distribution after initial drug administration. After a large or repeated dose, recovery relies more on elimination

**Rocuronium has lower molar potency (requires a larger mg/kg dose) and in effect has faster onset (i.e. it equilibrates faster from plasma to the neuromuscular junction)

Monitoring Neuromuscular Blockade

Monitoring Neuromuscular Blockade

- Document return of adequate neuromuscular function
- Determine dosing during prolonged administration
- Guides neuromuscular blockade reversal
- The train-of-four (TOF) ratio is the common modality of monitoring nondepolarizing NMBA. The number of twitches and the ratio between the 4th and 1st twitch are measured with the TOF.

Monitoring Neuromuscular Blockade

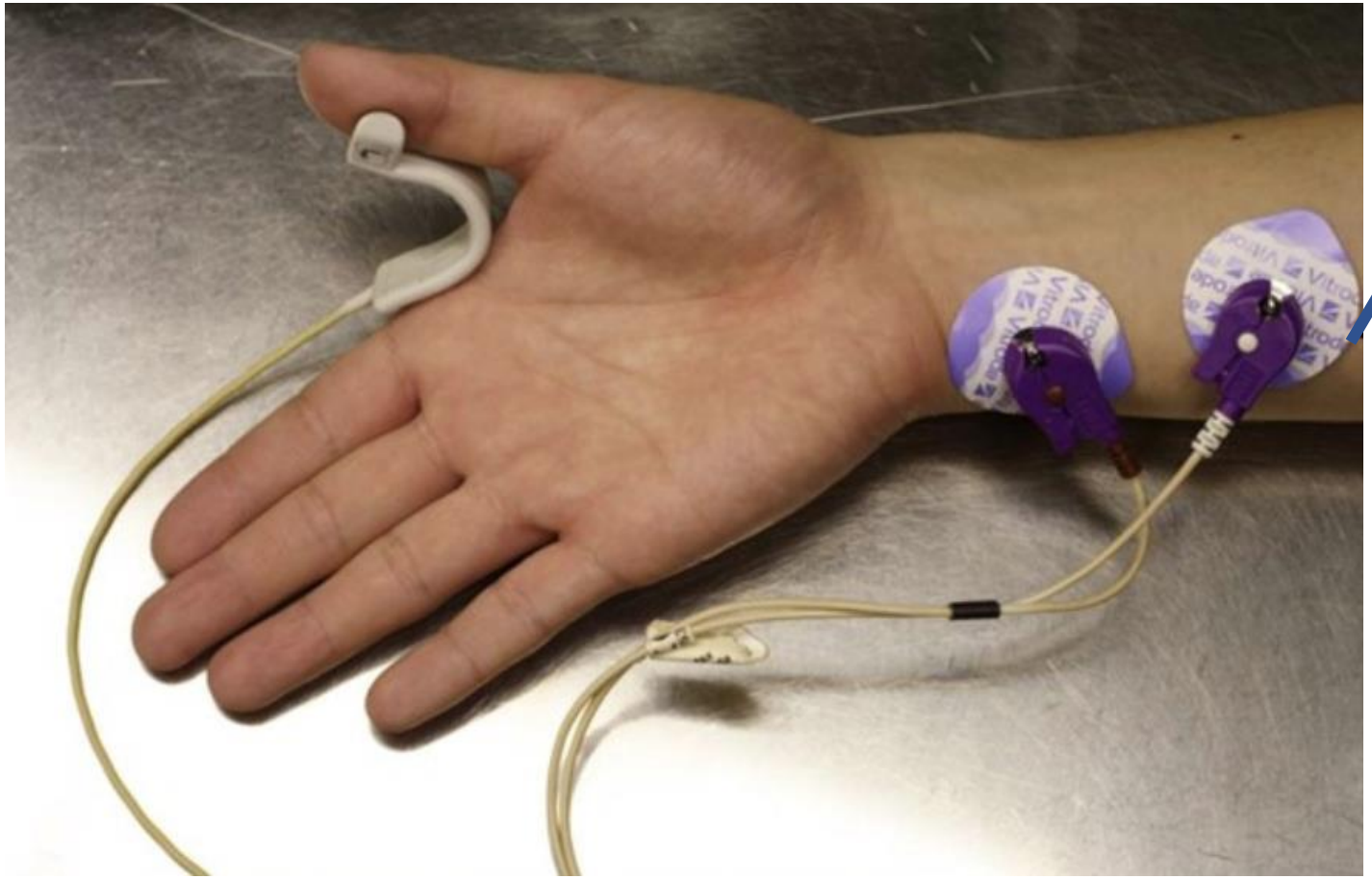
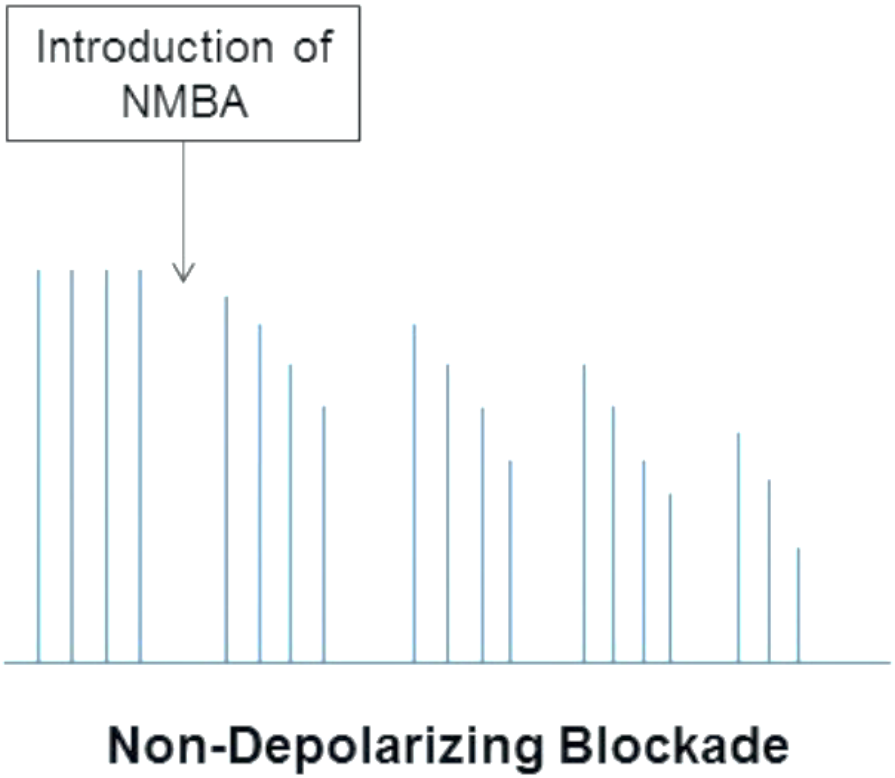
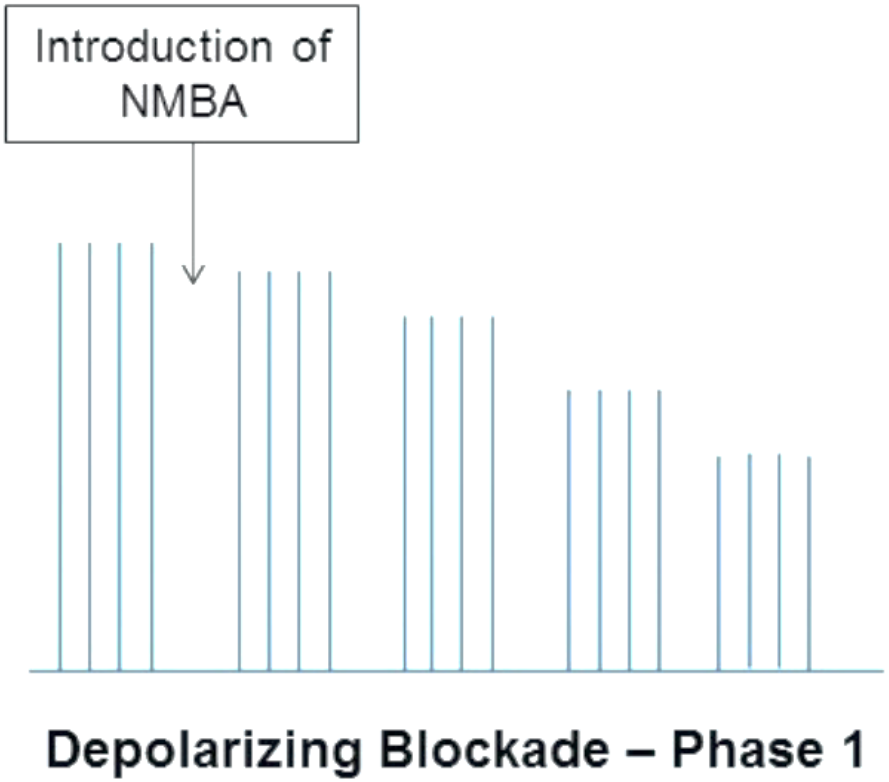


Image source – Wikimedia Commons

Train of Four Monitoring





McGrath CD, Hunter JM. Monitoring of neuromuscular block. Contin Educ Anaesth Crit Care Pain. 2006;6:7-12.

Reversal Agents

Reversal of Neuromuscular Blockade

- Reversal agents are commonly administered at the end of surgery
  - Facilitate extubation
  - Reduce operating room time
- Patients considered fully reversed and able to protect airway with TOF ≥ 0.9

1. Zhang B, Hepner DL, Tran MH, Friedman M, Korn JR, Menzin J. Neuromuscular blockade, reversal agent use, and operating room time: retrospective analysis of US inpatient surgeries. Curr Med Res Opin. 2009; 25: 943-50.
2. Srivastava A, Hunter JM. Reversal of neuromuscular block. Br J Anaesth. 2009; 103: 115-29.
3. Murphy GS, Szokol JW, Marymount JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the post anesthesia care unit. Anesth Analg. 2008; 107: 130-7.
4. McGrath CD, Hunter JM. Monitoring of neuromuscular block. Contin Educ Anaesth Crit Care Pain. 2006; 6: 7-12.

Reversal Agents

- Two classes based on mechanism of action
- ↑Ach – cholinesterase inhibitors
  - Neostigmine, pyridostigmine
- Chelation of agent with cyclodextrin
  - Sugammadex (Bridion)

1. Srivastava A, Hunter JM. Reversal of neuromuscular block. Br J Anaesth. 2009; 103: 115-29.
32. Nair VP, Hunter J. Anticholinesterases and anticholinergic drugs. Cont Educ Anaesth Crit Care & Pain. 2004;4(5): 164-168.

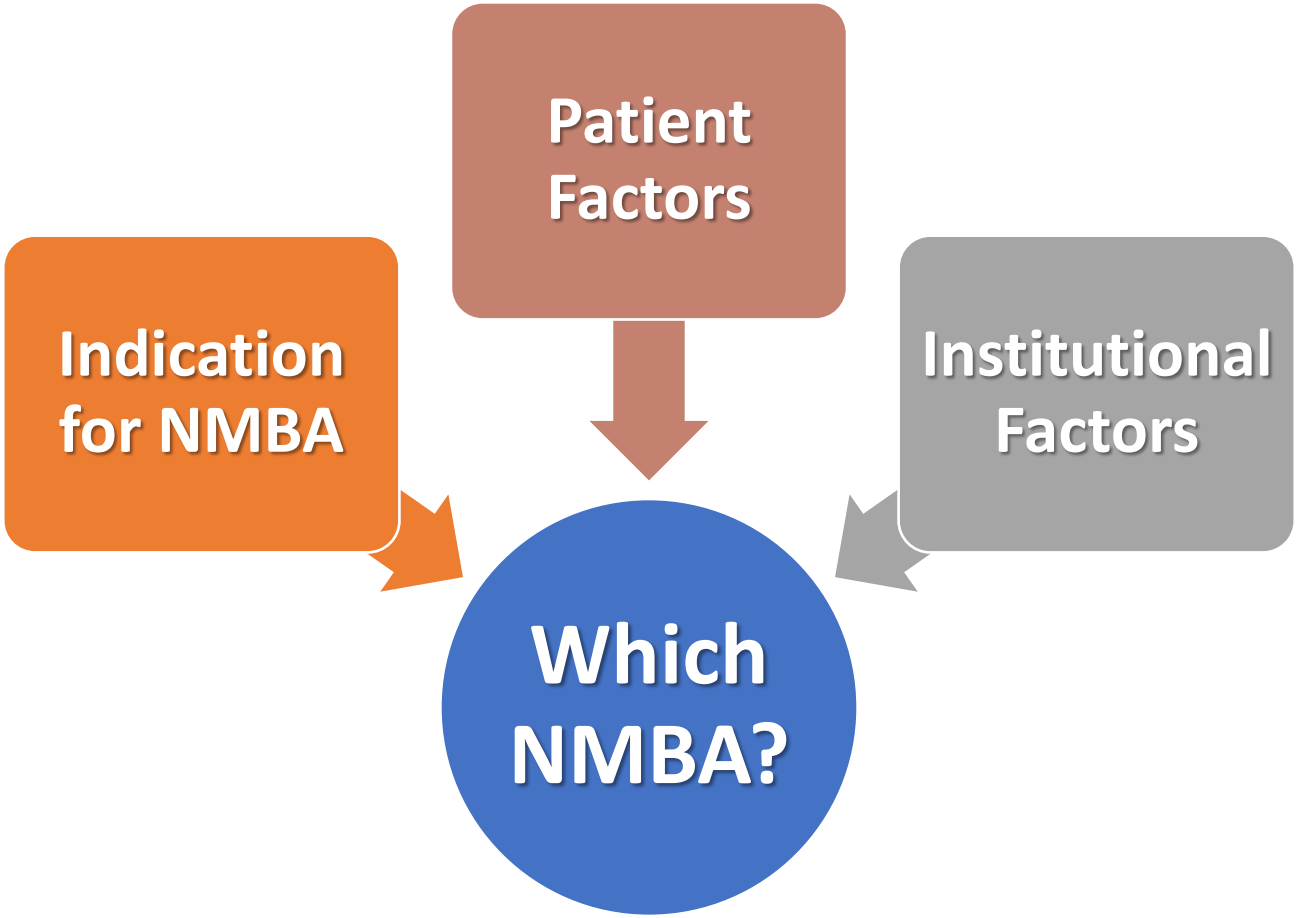
Acetylcholinesterase Inhibitor

- Less acetylcholinesterase working more Ach in NMJ overcome competitive inhibition by rocuronium & exhibit stronger muscle firing.
- Cholinesterase inhibitor-based reversal should not be given until spontaneous recovery has started.
  - Due to theoretically paradoxically slow recovery if given too early
- Always combine cholinesterase inhibitors with an anticholinergic
  - Cholinesterase inhibitors can cause muscarinic vagal side effects (eg. bradycardia, GI stimulation, bronchospasm) due to ↑ ACh activity at parasympathetic muscarinic receptors.
- Neostigmine with glycopyrrolate is most commonly used in the OR.
  - 40-50 mcg/kg of neostigmine is appropriate for most instances.
  - There is a ceiling effect. Do not give >70mcg/kg of neostigmine.
  - Dose of glycopyrrolate is 1/5 of the neostigmine dose (eg. 3mg neostigmine with 0.6mg glyco)

Sugammadex

- A modified γ-cyclodextrin with a hollow truncated core that traps aminosteroid class (rocuronium & vecuronium) for a more rapid and effective blockade reversal
- Very expensive
- Examples of indications to use sugammadex:
  - "Cannot intubate, cannot ventilate": after receiving a 1.2mg/kg dose of rocuronium, a 16mg/kg dose of sugammadex decreases time to full recovery from 122 minutes to <2 minutes.
  - For surgery during pregnancy it may be preferable to use sugammadex rather than neostigmine as sugammadex does not cross the placenta.

Choosing an NMBA



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- Sokół-Kobielska, E. Sugammadex — indications and clinical use. Anaesthesiol Intensive Ther. 2013 Apr-Jun;45(2):106-10.
- Stoelting RK and Miller RD. Basics of Anesthesia, 4th ed. Philadelphia: Churchill Livingstone, 2000.