Drugs used in Anesthesia

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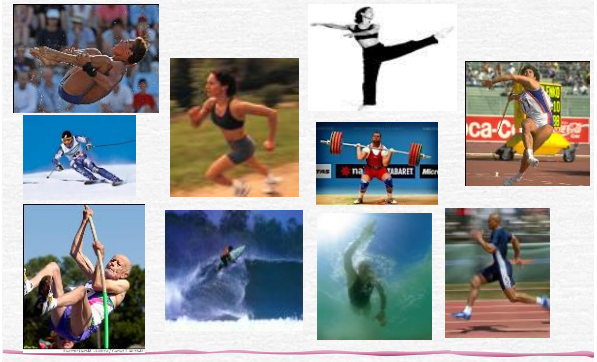
Objectives

- General anesthetics
- Muscle relaxants and cholinesterase inhibitors
- Analgesics and opioid antagonists
- Local anesthetics
- Other drugs










On-call duty

- Emergency call from the ED
  - 40-year-old man
  - Terrorist attack – Bomb blast
  - Anesthesiologist required – possible difficult airway
  - ETA: 6 min

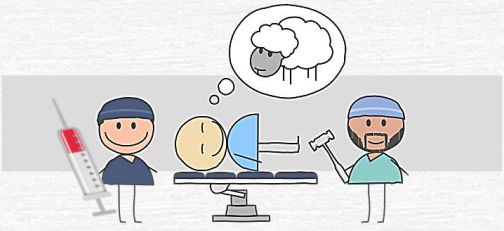

Drugs used in Anesthesia

- To produce a state of prolonged full surgical (or not) anesthesia reliably and safely
- Variety of drugs is needed – may be fatal
- Advanced Life Support training is **compulsory**

Drugs used in Anesthesia

- Special precautions and close monitoring of the patient are required
- **Induction** – **Maintenance** – **Emergence**
- Ensuring unconsciousness, amnesia, analgesia, loss of reflexes of the autonomic nervous system, and paralysis of skeletal muscles… when needed

Intravenous anesthetics



The ideal IV agent

- Rapid onset of action
- Quickly cleared from the bloodstream and central nervous system (CNS)
- Facilitates control of the anesthetic state (e.g., allowing titration of effect)
- Protects vital tissues
- Has other desirable pharmacologic effects (e.g., an antiemetic effect)
- Does not affect the circulatory system or cause other adverse effects
- Is inexpensive

Intravenous anesthetics

- Etomidate, midazolam, propofol, thiopental
  - Act by enhancing the activity of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the CNS
- Ketamine
  - Antagonizes the effect of the excitatory neurotransmitter N-methyl-D-aspartate (NMDA) on NMDA receptors
- Opioid agonists
  - Stimulate opioid receptors

Benzodiazepines – Midazolam

- Several uses
  - Pre-anesthetic sedation, anesthesia induction, sedation in ICU, sedation in combination with regional anesthesia (± ketamine)
  - 0.3-0.35 mg/kg IV injection over 20-30 seconds (reduce by 20-50% for acutely ill, chronically ill, or geriatric patients)
  - High fat solubility

Benzodiazepines – Midazolam

- Elimination half-live: 1.7-2.6 h
- Dose-dependent respiratory depression
- Minimal cardiovascular suppression
- ↓ cerebral O_2 consumption, cerebral blood flow, and intracranial pressure
- Anxiolytic, amnesic, anticonvulsant and muscle relaxant properties

Ketamine

- Anesthesia persists for up to 15 min after a single intravenous injection
- Rapid brain uptake, Dissociative anesthesia
- Profound analgesia, bronchodilation
- Direct stimulation of the sympathetic system
  - ↑ Blood pressure, heart rate, cardiac output
  - ↑ Cerebral blood flow, intracranial pressure, and cerebral O_2 consumption

Ketamine

- May be associated with hallucinations and other emergence reactions
- 1-4.5 mg/kg slow IV once, ***but***:
  - Use subanesthetic concentrations
  - ~0.3 mg/kg if adjuvant drugs are used (e.g. midazolam)
    - Maintains breathing

Propofol

- High fat solubility
- Rapid onset of action – causes loss of consciousness within 30-45 sec
- Induction: 1-2.5 mg/kg ***slow*** IV
- Infusion: 0.1-0.2 mg/kg/min
- Rapid metabolism in the liver
  - Recovery is rapid even after prolonged administration

Propofol

- Rapid metabolism in the liver
  - Recovery is rapid even after prolonged administration
- Causes vasodilation and negative inotropy
- May not be tolerated well by patient with severe circulatory compromise
- No provision of analgesia

Etomidate

- Loss of consciousness within 30 sec
- Minimal effect on blood pressure and cardiac output
- Reduces cerebral blood flow and intracranial pressure
  - Cerebral perfusion pressure (CPP) remains unchanged

Etomidate

- Suppression of adrenal cortex
  - Inhibition of enzymes involved in the synthesis of cortisol and aldosterone
- 0.3-0.6 mg/kg over 30-60 sec

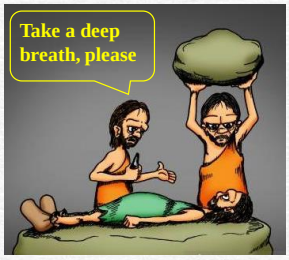
Barbiturates – Thiopental

- May be used alone to produce anesthesia
- Rapidly crosses the blood-brain barrier – Loss of consciousness within 30-60 sec
  - Excitement does not usually occur
  - Anesthesia persists for about 4-7 min
  - Can produce hypotension
- Large or repeated doses severely depress respiration and delay recover

Barbiturates – Thiopental

- Can reduce:
  - Intracranial pressure and cerebral metabolic rate of O_2 (cerebral autoregulation is maintained – CPP unchanged)
  - Renal blood flow and glomerular filtration
- Use 2.5% solution (3-6 mg/kg)

Inhalational anesthetics



Inhalational anesthetics

- Are used for the induction and maintenance of general anesthesia as well as sedation
- Cause respiratory depression, arterial hypotension, ↓ cerebral metabolic demand, ↑cerebral blood flow
- Nitrous oxide, Desflurane, Sevoflurane, Isoflurane, Enflurane, Halothane

Inhalational anesthetics

- The inhaled anesthetics affect many receptors (e.g., $GABA_A$, glycine, acetylcholine, serotonin, NMDA) in manners that plausibly could explain anesthesia
- Which receptors mediate anesthesia remains unclear

Inhalational anesthetics

- The ideal anesthetic agent produces anesthesia while allowing the use of a high concentration of oxygen
- Minimum alveolar concentration (MAC)
  - At one atmosphere
  - Abolishes movement in response to a noxious stimulus in 50% of subjects
  - Standard definition of inhaled anesthetic potency

Neuromuscular Blocking Agents

Neuromuscular Blocking Agents

- Interrupt transmission of nerve impulses at the skeletal neuromuscular junction
- Competitive, stabilizing blockers (non-depolarizing agents)
- Non-competitive, depolarizing agents (depolarizing agents)
- Both prevent acetylcholine from triggering the muscle contraction

Rocuronium

- Facilitates both rapid sequence and routine tracheal intubation
- Provided skeletal muscle relaxation during surgery or mechanical ventilation
- Tracheal Intubation: 0.45-0.6 mg/kg IV
  - Continuous infusion: 0.01-0.012 mg/kg/min IV
- Rapid Sequence Induction
  - 0.6-1.2 mg/kg IV

Rocuronium

- Sugammadex: Elective relaxant binding agent for reversal of neuromuscular blockade induced by rocuronium in adults
- Doses/timing of administration is based on:
  - Monitoring for twitch responses
  - The extent of spontaneous recovery that has occurred
- 2-16 mg/kg as single IV bolus over 10 sec

Cisatracurium

- Facilitates tracheal intubation and provides skeletal muscle relaxation during surgery or mechanical ventilation
- Initial intubating dose: 0.15-0.2 mg/kg IV
- Maintenance dose: 0.03 mg/kg IV
  - 40-50 min following initial dose of 0.15 mg/kg
  - 50-60 min following initial dose of 0.2 mg/kg

Cisatracurium

- IV infusion (extended surgery or in ICU)
  - 3 mcg/kg/min post-bolus to prevent rapid spontaneous recovery of neuromuscular blockade, **THEN**
  - 1-2 mcg/kg/min for maintenance
  - Reduced infusion rate (by 30-40%) may be required when given during stable inhalational anesthesia

Cisatracurium

- Reversal with a cholinesterase inhibitor
- 0.04-0.08 mg/kg Neostigmine
  - Max: 0.07 mg/kg or 5 mg in total
- In conjunction with:
  - 0.2 mg Glycopyrrolate **or**
  - 0.4 mg Atropine

} **Per mg of neostigmine**

Succinylcholine

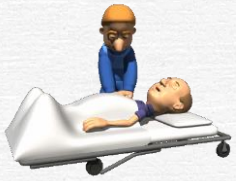
- When rapid onset and brief duration is needed (e.g. intubation, endoscopies, etc.)
- IV: 0.3-1.1 mg/kg
  - Onset: 30-60 sec; Duration: 4-6 min
- IM: 3-4 mg/kg IM x1 dose
  - Onset: 2-3 min; Duration: 10-30 min
- Atropine may reduce vagally mediated bradycardia/hypotension/drooling

Succinylcholine

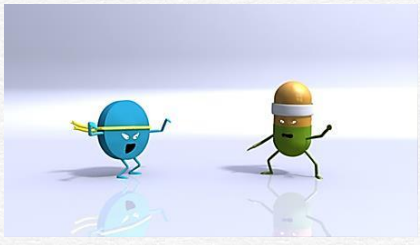
- Prior administration of "defasciculating" dose of non-depolarizing neuromuscular blocker
  - e.g. 0.01 mg/kg IV rocuronium
  - Prevents muscular fasciculations that may increase intracranial or intraocular pressure
- May experience increased sensitivity with electrolyte disorders (K^+, Mg^{++}, Ca^{++})

Succinylcholine

- Rhabdomyolysis with hyperkalemia
- Ventricular dysrhythmias and cardiac arrest



Opioids



Opioids

- Bind to specific receptors in the CNS and other tissues → Analgesia
- Four major types of opioid receptors have been identified: μ, κ, δ, σ
- Generally, opioids are metabolized in the liver
- Morphine, pethidine, fentanyl, remifentanil

Opioids

- Non-significant cardiovascular effects
  - Bradycardia (→ hypotension)
  - Pethidine: tachycardia
  - Morphine and pethidine may cause a greater decrease in blood pressure due to histamine release
- Respiratory depression

Opioids

- Reduces cerebral blood flow, cerebral O_2 consumption, and intracranial pressure
- Dizziness, lethargy, apathy, euphoria, suppression of cough reflex, itching, nausea and vomiting

Opioids

- Fentanyl-induced chest wall rigidity
- ↓ gastrointestinal motility, lower oesophageal sphincter relaxation, delayed gastric emptying

	Loading Dose	Maintenance Dose		Comments
		Bolus	Infusion	
Fentanyl	2-6 µg/kg	25-50 µg/kg	0.5-5.0 µg/kg/hr	Risk of significant depression of spontaneous ventilation
Alfentanil	25-50 µg/kg	5-10 µg/kg	0.5-2 µg/kg/min	Propofol decreases elimination clearance and distribution
Sufentanil	0.25 - 2µg/kg	0.1 - 0.25 µg/kg	0.5-1.5 µg/kg/hr	
Remifentanil	1 - 2 µg/kg		0.1-1.0 µg/kg/min	During emergence and post-operatively alternative analgesia should be administered or low-dose infusion continued
Morphine	Premed: 100-1000 µg/kg	50-100 µg/kg		Postop: 0.03-0.15 mg/kg

Benzodiazepine antidote - Flumazenil

Benzodiazepine antidote – Flumazenil

- Reversal of conscious sedation and general anesthesia
  - 0.2 mg IV over 15 sec
  - If after 45 sec no response, administer 0.2 mg again over 1 min; may repeat at 1 min intervals; not to exceed 4 doses (1 mg)
  - If resedation occurs, may repeat doses at 20-min intervals; not to exceed 1 mg/dose or 3 mg/h

Benzodiazepine antidote – Flumazenil

- Benzodiazepine overdose
  - 0.2 mg IV over 15-30 sec
  - IF no response after 30 sec → 0.3 mg over 30 sec 1 min later
  - IF no response → repeat dose of 0.5 mg IV over 30 sec at 1-min intervals to max cumulative dose of 3 mg/h
  - In resedation occurs, may repeat dose at 20-min intervals if needed; not to exceed 1 mg (administered as 0.5 mg/min) administered at any one time and no more than 3 mg/h
  - Rarely patient may require titration up to total dose 5 mg; If no response after 5 min, sedation unlikely to be secondary to benzodiazepines

Opioid antagonists – Naloxone

Opioid antagonists – Naloxone

- 0.1-0.2 mg IV q2-3min to desired degree of reversal (e.g., adequate ventilation and alertness without significant pain)
- May repeat within 1-2h intervals depending on amount, type (e.g., short or long acting) and timing of last dose administered
- Supplemental IM doses have produced longer lasting effects

Opioid antagonists – Naloxone

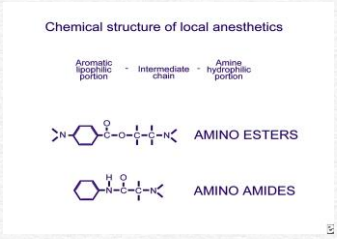
- Indicated for the complete or partial reversal of opioid depression (including respiratory depression) induced by natural and synthetic opioids
- 0.4-2 mg IV/IM/SC; repeat q2-3min when needed; not to exceed 10 mg (0.01 mg/kg)
- Consider other causes of respiratory depression if desired response not achieved after administering 10 mg cumulative total
- For chronic opioid abuse → smallest doses (0.1-0.2 mg) to avoid acute withdrawal; titrate to reversal of respiratory depression
- Following reversal, additional dose(s) may need to be administered at later interval (i.e., 20-60 min) depending on type and duration of opioid

Other analgesics

- Paracetamol
- Nonsteroidal anti-inflammatory drug (NSAID)
  - Acetic acids (e.g. diclofenac - Voltaren®)
  - COX-2 inhibitors (e.g. celecoxib, parecoxib - Dynastat®)
  - Oxicams – unselective inhibitors of COX enzymes (e.g. lornoxicam - XEFO®)

Local anesthetics

Local anesthetics



Local anesthetics

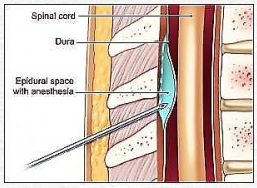
- Produce anesthesia by inhibiting excitation of nerve endings or by blocking conduction in peripheral nerves
- This is achieved by anesthetics reversibly binding to and inactivating Na^+ channels
- Na^+ influx is necessary for the depolarization of nerve cell membranes and subsequent propagation of impulses along the course of the nerve

Local anesthetics

- Subarachnoid
- Epidural
- Local

Local anesthetics

Drug	Onset	Maximum Dose (with Epinephrine)	Duration (with Epinephrine)
Lidocaine	Rapid	4.5 mg/kg (7 mg/kg)	120 min (240 min)
Mepivacaine	Rapid	5 mg/kg (7 mg/kg)	180 min (360 min)
Bupivacaine	Slow	2.5 mg/kg (3 mg/kg)	4 hours (8 h)
Ropivacaine	Medium	2-3 mg/kg	3 hours (6 h)
Levobupivacaine	Medium	2.0 mg/kg or 400mg in 24 hrs	4-6 hours (8-12 h)
Procaine	Slow	8 mg/kg (10 mg/kg)	45 min (60 min)
Chloroprocaine	Rapid	10 mg/kg (15 mg/kg)	30 min (60 min)
Etidocaine	Rapid	2.5 mg/kg (4 mg/kg)	4 hours (8 h)
Prilocaine	Medium	5 mg/kg (75 mg/kg)	90 min (360 min)
Tetracaine	Slow	1.5 mg/kg (2.5 mg/kg)	3 hours (10 h)



Local anesthetics

- Adverse reactions occur primarily in the CNS (neurotoxicity) and cardiovascular system (myotoxicity) because these tissues are also composed of excitable membranes, the target of local anesthetic action

Local anesthetics

- Central nervous system
  - Circumoral and/or tongue numbness, metallic taste, lightheadedness, tinnitus, or double vision
  - Drowsiness, slur speech, nystagmus
  - Anxious patient with fine tremors of the muscles of the hands and/or face → Grand mal seizure
  - Ultimately, the patient may experience generalized CNS depression leading to hypoxia, acidosis, and respiratory arrest

Local anesthetics

- Cardiovascular system
  - Decrease the rate of depolarization of cardiac tissue
  - Decreased amplitude of the cardiac action potential and reduced conduction velocity
  - Hypotension
    - Direct vasodilating effects of local anesthetics on peripheral arteriolar smooth muscle
  - Negative inotropic effects
    - Bradycardia, ventricular fibrillation, or asystole

Local anesthetics

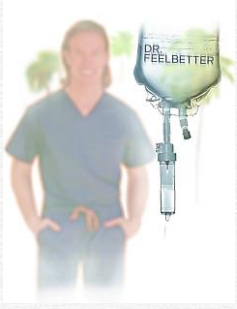
- Local anesthetic systemic toxicity (LAST)
  - Usually results from iv or intra-arterially injection of regional anesthetics
  - Involves systemic absorption of the drug, with resultant neurotoxicity and cardiotoxicity
  - Advanced Life Support **+ INTRALIPID®**

Lipid Emulsion 20% (Precise volume and flow rate are not crucial)	
Greater than 70 kg patient	Less than 70 kg patient
Bolus 100 mL Lipid Emulsion 20% rapidly over 2-3 minutes • Lipid emulsion infusion 200-250 mL over 15-20 minutes	**Bolus 1.5 mL/kg Lipid Emulsion 20%** rapidly over 2-3 minutes • Lipid emulsion infusion ~0.25 mL/kg/min (ideal body weight)
If patient remains unstable: • Re-bolus once or twice at the same dose and double infusion rate; be aware of dosing limit (12mL/kg) • Total volume of lipid emulsion can approach 1 L in a prolonged resuscitation (e.g., > 30 minutes)	

Other drugs

Other drugs

- Vasopressors / Inotropes / β_2-adrenergic-agonists
  - Norepinephrine, phenylephrine, epinephrine, dobutamine, isoprenaline
- β-blockers
  - Esmolol, propranolol
- Vasodilators
  - Nitroglycerin, nitroprusside
- Other (antiemetics, PPIs, etc.)



MCQ 1

- A 28-year-old patient has severe laryngospasm after extubation of the trachea following general anesthesia. Administration of 100% oxygen using continuous positive airway pressure does not improve symptoms. SpO_2 is 75%. Which of the following is the most appropriate immediate management?
  1. Laryngeal mask airway
  2. Lidocaine
  3. Racemic epinephrine
  4. Succinylcholine
  5. Cricothyroidotomy

MCQ 2

- Which of the following is correct regarding rocuronium?
  1. The dose for rapid sequence induction is 0.6-1.2 mg/kg IV
  2. It is a vasodilator
  3. The dose for tracheal intubation is 5-7 mg/kg IV
  4. Can be administered sublingually in children
  5. Does not facilitate routine tracheal intubation

MCQ 3

- A 70-kg 78-year-old man undergoing small-bowel resection during anesthesia with desflurane in oxygen becomes hypotensive and develops frothy pink sputum in the endotracheal tube. Heart rate is 50 bpm, blood pressure is 75/60 mmHg, pulmonary artery occlusion pressure is 22 mmHg, and cardiac output is 1.7 L/min. The most appropriate initial step in management is administration of which of the following?
  1. Albunin
  2. Digoxin
  3. Dobutamine
  4. Esmolol
  5. Nitroglycerin

MCQ 4

- Which of the following is correct regarding propofol?
  1. It is usually administered after emergence and at the Postanesthesia Care Unit
  2. Large iv doses markedly increase arterial blood pressure
  3. It is characterized by slow onset of action
  4. The dose for induction of anesthesia is 1-2.5 mg/kg slow IV
  5. It is metabolized in the kidney

MCQ 5

- A 75-year-old man with aortic stenosis and coronary artery disease has a pre-induction heart rate of 68 bpm and blood pressure of 125/70 mmHg. After induction of anesthesia with midazolam, fentanyl, and rocuronium, heart rate is 90 bpm and blood pressure is 85/45 mmHg. ECG shows a new ST-segment elevation in lead II. Which of the following is the most appropriate initial management?
  1. Ephedrine
  2. Epinephrine
  3. Esmolol
  4. Nitroglycerin
  5. Phenylephrine