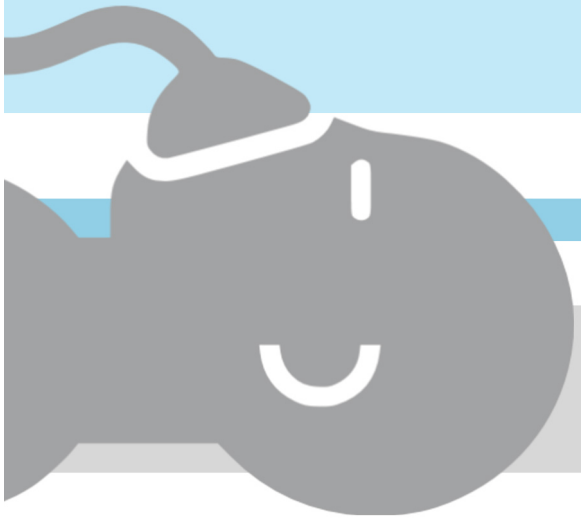

ANESTHESIA

(4) Pharmacology of Anesthesia

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Revised by:

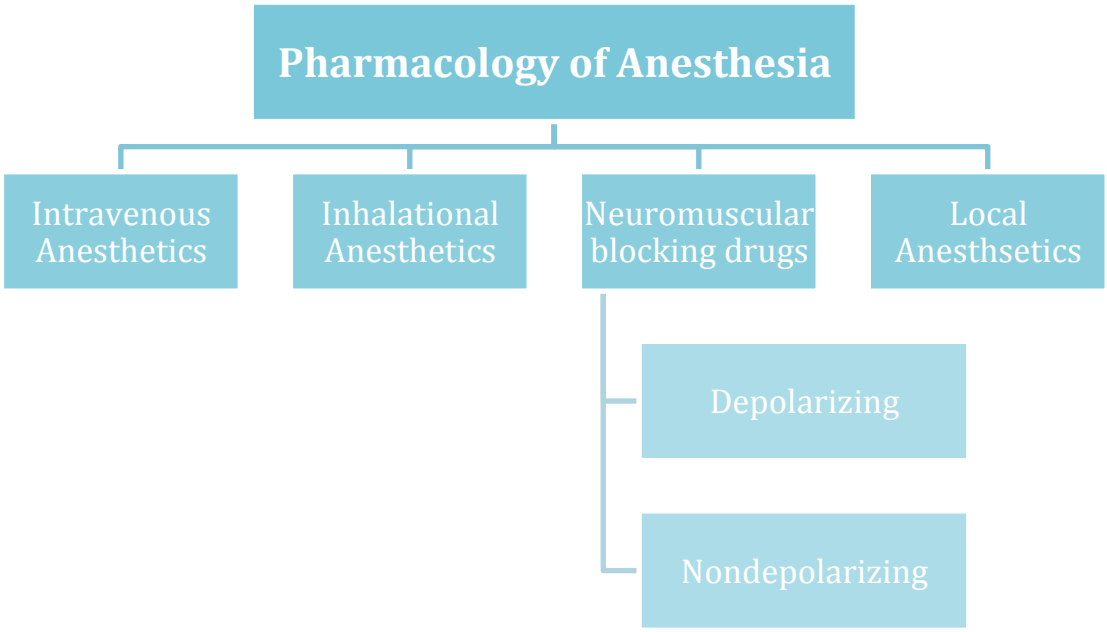
Lulu Alobaid.

Doctor's note Team's note Not important Important 431 teamwork

(431 teamwork do not highlight it in yellow, but put it in a yellow "box")

Objectives:

Not given.



Many thanks to 431 team for their notes!

The doses are not required according to dr. Jumanna

General Anesthesia

Inhalation anesthetics are usually administered for maintenance of general anesthesia but also can be used for induction, especially in pediatric patients.

-Anesthesia booklet

Background:

- General anesthesia: triad of
  - ***Amnesia***
  - ***Analgesia***
  - ***Muscle relaxation***

1. Intravenous anesthetics:
   a. Benzodiapines
   b. Propofol
   c. Etomidate
   d. Dexmetomidine
   e. Opioids
2. Inhalational:
   a. Nitrous oxide
   b. Desflurane
   c. Sevoflurane
   d. Halothane
3. Neuromuscular blocking drugs

IV anesthetics

(a) Benzodiazepines:

- Examples: (i) Diazipam (ii) midazolam (iii) lorazepam.
- **Primary uses:** sedation, amnesia, anxiolysis for premedication or as adjuncts to general anesthesia.

As premedication, you can give a tablet of midazolam for anxiolysis and as adjunct during induction but not on its own; midazolam is mainly a SEDATIVE. Ex: pt comes in for laparotomy and you give him midazolam. He will sleep but will jump when you touch him because there's no analgesia.

- **Mechanism.** Enhance inhibitory neurotransmission by increasing the affinity of GABAA receptors for GABA.

❖ Pharmacokinetics

- Effects are terminated by redistribution. Short duration of action.
- All are metabolized in the liver. Liver disease prolongs duration of action.
- Hydroxymidazolam cause sedation in Pt with renal failure.
- Diazepam clearance is reduced in the elderly. Metabolism slows with aging.

❖ Pharmacodynamics

- **CNS**
  - Amnestic, anticonvulsant, anxiolytic, and sedative-hypnotic (dose-dependent manner). Higher dose = more sedation.
  - No analgesia.
- **Cardiovascular system**
  - Mild systemic vasodilation and ↓ in cardiac output. Hypotension mild in this group.
  - HR is usually unchanged.
- **Respiratory system**
  - Mild dose-dependent ↓ in RR and TV.
  - Respiratory depression may be more if administered with an *opioid*. Like synergism.

❖ Types

(i) Midazolam (*Dormicum*) :

- Water soluble, so drug of choice for IV administration. Many routes available.
- More rapid onset and more rapid elimination
- The most potent amnestic

(ii) Diazepam (*Valium*):

Water-insoluble, so IV use can cause local irritation/pain

(iii) Lorazepam (Ativan):

- water-insoluble,

Adverse effects:

- **Drug interactions.**
  with anticonvulsant (valproate) +diazepam
- **Pregnancy and labor**
  - Risk of cleft lip and palate in the first trimester.
  - CNS depression in the neonate. Crosses placenta. Avoid with C/S.
- **Superficial thrombophlebitis and injection pain** by diazepam and lorazepam.

(B) Flumazenil:

BEN IS OFF WITH FLU: Flumazinil is the antidote to benzodiazepines. If we sedate the patient and we have a hard time waking them up, we administer flumazenil.

- **A competitive antagonist at the benzodiazepine binding site of GABAA receptors in the CNS.**
  - Reversal of sedative effects occurs within 2 min; peak effects at 10 min.
  - **Half-life is shorter** than the benzodiazepines. So if you use it to reverse effect of benzodiazepines you'll need repeated dosing.
  - Metabolized to inactive metabolites in the liver.
  - **Dose**. 0.3 mg IV every 30 to 60 seconds (to a maximum dose of 5 mg).
  - **Contraindicated** in Pt with tricyclic antidepressant overdose and in those receiving benzodiazepines for the control of seizures or elevated ICP or long-term treatment with benzodiazepines.

(c) Propofol: 1% isotonic oil-in-water emulsion, which contains egg lecithin, glycerol, and soybean oil.

In KKUH propofol is the most commonly used one. It used to be thiopental –used to control seizures- which is cheaper. Advantages: Rapid induction and recovery. Antiemetic properties. Disadvantages: **Pain on injection.** Resp. depression and apnea. Bradycardia and hypotenstion.

Primary uses:

- A sedative/hypnotic in OR & (ICU)

- Induction
- Maintenance of anesthesia (TIVA) total intravenous anesthesia.

Mechanism: Facilitates inhibitory neurotransmission by enhancing the function (GABAA) receptors in CNS.

Pharmacokinetics:

Hepatic and extrahepatic metabolism to inactive metabolites which are renally excreted. Onset after 30 secs so good for abscess I&D.

Pharmacodynamics:

- **CNS**
  - **Induction**: rapid onset of unconsciousness (30 to 45 seconds), followed by a rapid termination of effect by redistribution.
  - **Emergence** is rapid -rapid recovery.
  - Weak analgesic effects.
  - ↓ (ICP) and ↓ (CPP) due to markedly ↓ (MAP). Anticonvulsant. Antiemetic > given post op to reduce n/v.
  - Less (PONV) occurs.
  - **Cardiovascular system**
  - Dose-dependent ↓ in preload, afterload, and contractility lead to ↓ in (BP) and COP.
  - **Hypotension** may be marked in hypovolemic, elderly, or hemodynamically compromised patients.
  - Heart rate (HR) is minimally affected, and baroreceptor reflex is blunted.
  - **Respiratory system**
  - Dose-dependent decreases in (RR) and (TV).
  - ↓Ventilatory responses to hypoxia and hypercarbia.

Dosage and administration.

- Induction: IV 1-2.5mg/kg
- Sedation: IV 25-100 µ/kg/min. Given to anxious patients in small doses.
- *Titrate with incremental doses in hypovolemic, elderly, or hemodynamically compromised patients or if administered with other anesthetics.* To reduce degree if hypotension but ketamine is better if available.

Adverse effects:

MCQ: Patient taking propofol, fentanyl and succinylcholine and felt some pain during injection; which drug caused this? Propofol is famous for this. When used alone it causes venous irritation. Add lidocaine.

- **Venous irritation.**
- **Bacterial growth**
- **Lipid disorders.** used cautiously in disorders of lipid metabolism (e.g., hyperlipidemia and pancreatitis).
- **Myoclonus and hiccups**. Happens more with Etomidate.

Propofol infusion syndrome: a rare fatal disorder that occurs in critically ill patients (usually children) subjected to prolonged, high-dose propofol infusions. **(Rhabdomyolysis, metabolic acidosis, cardiac failure, and renal failure).**

(c) Barbituates:

- Such as **thiopental and methohexital** (highly alkaline).

Mechanism:

- Facilitate inhibitory neurotransmission by enhancing GABAA receptor function.
- Inhibit excitatory neurotransmission via glutamate and nicotinic acetylcholine receptors.

Primary Use: Induction of anesthesia. Maintenance causes prolonged effect. Used with epileptics.

Advantages:

- Rapid onset (30 - 45 sec)
- Short duration (5 – 8 min) initial dose; redistributed from brain to muscle.

Pharmacokinetics:

- Hepatic metabolism.
- Multiple doses or prolonged infusions may produce prolonged sedation or unconsciousness.

Pharmacodynamics:

CNS

- Dose-dependent CNS depression.
- ↓ in (CMRO2) -cerebral metabolic rate- cause ↓ in ICP and (CBF). Most IV anesthetics reduce ICP except ketamine.

Cardiovascular system

- Depress myocardial contractility, leading to dose-dependent ↓ in BP and cardiac output.
- Baroreceptor reflexes remain largely intact.

Respiratory system

- Dose-dependent decreases in RR and TV.
- Apnea may result for 30 to 90 seconds after an induction dose.
- Laryngeal reflexes remain more intact compared with propofol > higher incidence of cough and laryngospasm. Ketamine should be used instead in case of bronchial asthma.
- Worsens glaucoma.

Adverse effects:

- **Allergy.**
- **Absolutely contraindicated in Porphyria.**
- **Venous irritation and tissue damage**
  - Thiopental can cause severe pain and tissue necrosis if injected extravascularly or intra-arterially. If intra-arterial administration occurs, heparin, vasodilators, and regional sympathetic blockade may be helpful in treatment.
- **Myoclonus and hiccups**. More with methohexital.

Dosage and administration:

- Induction: IV 3-6 mg/kg
  - sedation IV 0.5-1.5 mg/kg
- *N.B. Reduce doses in hypovolemic (these drugs cause myocardial depression), elderly (reduced liver function), or hemodynamically compromised patients.*

Disadvantages:

- No analgesia. Can we use it without opioids? Mostly no.
- Decreased blood pressure.
- Decreased RR and tidal volume/apnea.
- Coughing, layrngospasm, bronchospasm (intact reflexes)

(d) Ketamine: old drug

- A sedative-hypnotic agent with potent analgesic properties. Even with subanesthetic –small- doses.

Primary uses:

- Induction of GA. In patients with CVS problems.
- Sedation and analgesia.

Mechanism: mainly attributed to noncompetitive antagonism of NMDA receptors in the CNS.

Pharmacokinetics:

- Unconsciousness in 30 to 60 s after an IV.
- Terminated by redistribution in 15 to 20 minutes.
- Metabolized rapidly in the liver to multiple metabolites, some of which have modest activity (e.g., norketamine -sedative).
- Elimination half-life is 2 to 3 hours.
- Repeated bolus doses or prolonged infusions result in accumulation.

Pharmacodynamics:

- **CNS**
  - Produces a "dissociative" state accompanied by amnesia and profound analgesia.
  - **Imp:** ↑ (CBF), ↑ (CMR), and ↑(ICP) pressure. Never in pts with head trauma/brain tumours.
- **Cardiovascular system**
  - ↑ HR, COP, and BP.
    - MCQ: Ketamine causes tachycardia and HTN.
    - This property is useful to correct low BP.
  - Used in hemodynamically compromised Pt. 2nd line.
- **Respiratory system**
  - Mild depression of (RR) and (TV).
  - Potent bronchodilator. Used in status asthmaticus.

- Laryngeal protective reflexes are maintained. Aspiration might still happen if on full stomach without an endotracheal tube.

Adverse effects:

- **Oral secretions.** Reduced by atropine/glycovirulate.
- **Emotional disturbance.** agitation & hallucinations. MCQ: hallucinations = ketamine. Remember drug abuse!
- **Muscle tone:** often increased.
- ↑ **ICP :** contraindicated in patients with head trauma or intracranial hypertension.

- **Ocular effects.** mydriasis, nystagmus, diplopia, and ↑ intraocular pressure. MCQ: NEVER in ophthalmic surgery.

(e) Etomidate:

Primary use: Induction in patients w/ cardiovascular problems.

Mechanism: Facilitates inhibitory neurotransmission by enhancing GABAA receptor function.

Pharmacokinetics:

- Effects of a single bolus dose are terminated by redistribution. (like propofol).
- Very high clearance in the liver and by circulating esterases to inactive metabolites. (rapid recovery).

Pharmacodynamics:

- ✓ **CNS**
  - ✓ No analgesic properties.
  - ✓ ↓ (CBF), cerebral metabolic rate, (CMR), and (ICP). Used with neurosurgery.
- ✓ **Cardiovascular system**
  - ✓ Minimal changes in HR, BP, and COP. The best for hemodynamic compromise. Doesn't affect baroreceptor function or sympathetic tone.
- ✓ **Respiratory system**
  - ✓ Dose-dependent ↓ in (RR) & (TV).
  - ✓ Transient apnea may occur.

Dosage and administration:

Induction: IV 0.2-0.5mg/kg
IM 3-5mg/kg

N.B. Useful for IM induction in patients with no IV access (e.g., children).

Adverse effects:

- ✓ **Myoclonus**. Very famous for it.
- ✓ **Nausea and vomiting**.
- ✓ **Venous irritation and superficial thrombophlebitis**
- ✓ **Adrenal suppression**; Very famous for it.
  - Inhibits 11β-hydroxylase. Avoid in adrenal insufficiency.
  - A single induction dose suppresses adrenal steroid synthesis for up to 24 hours. Not clinically significant in OR. Worse with larger doses.
  - Repeated doses or infusions is associated with increased mortality in ICU patients.

Advantages:

- Rapid induction + recovery.
- Ultra-short acting (5min).
- No CVS depression.

Advantages:

- Pain on injection, Involuntary muscle movement (myoclonus), Nausea and vomiting, Hiccups.
- Not analgesic.
- Adrenocortical suppression.

(f) Opioids:

- Opioids produce moderate sedation and **profound analgesia**. Mainly given for analgesia.
- They exert their effects by binding with opioid receptors in CNS (3 major opioid receptors **μ** (mu), **κ** (kappa), and **δ** (delta).
- **Meperidine (**pethidine, no longer used as it is less potent and causes convulsions but useful for pts with renal failure**), Morphine, Alfentanil, Fentanyl (**most commonly used**), Sufentanil, Remifentanil.**

Advantages:

- Minimal cardiac effects. Used in cardiac surgery and MI.
- No myocardial depression

Side effects : MORPHINES

- Miosis.
- Orthostatic hypotension.
- Respiratory depression.
- Pain supression.
- Histamine release – Some peripheral vasodilation and hypotension, itching.
- Nausea & vomiting -Stimulation of chemoreceptor trigger zone (CTZ).

- Euphoria.
- Sedation.
- Drowsiness or sedation,
- Chest wall rigidity. Hard to ventilate. Goes away after few mins.
- Bradycardia in large doses
- Constipation,
- Urinary retention & biliary colic,
- Slow gastric emptying.

<table>
<tr>
<td>1. Morhpine:
May produce hypotension and bronchoconstriction as a consequence of its histamine-releasing action.
Morphine may be a poor choice for a patient with renal failure.
Used in cardiac surgery.</td>
<td>2. Fentanyl most commonly used
A potent synthetic opioid agonist with between 100 times the analgesic potency of morphine.
Used for induction and maintenance of G.A and to supplement regional and spinal anesthesia.
Ability to maintain cardiac stability.
When analgesic effect fades the HR and BP will go up indicating the need to redose.
Supplements spinal/epidural analgesia > prolongs duration.</td>
</tr>
<tr>
<td>3. Sufentanil citrate (Sufenta)
10 times as potent as fentanyl
Rapid elimination,
Relatively more rapid recovery as compared with fentanyl.</td>
<td>4. Alfentanil
Shorter duration of action compared to fentanyl and sufentanil,</td>
</tr>
<tr>
<td colspan="2">5. Remifentanil (Ultiva)
Ultra short acting and rapidly cleared
widespread extrahepatic metabolism by blood and tissue nonspecific esterases.</td>
</tr>
</table>

Naloxone

- A specific opiate receptor antagonist, binding the receptor
- The effective dose is 1 to 4 μg/kg IV, and the duration of action is 30 to 45 min.
- Dose may need to be repeated or an infusion. Half life short.
- Antidote to reverse respiratory depression *and* analgesia. So if you use it the pt may breathe freely but will feel pain.
- If you can't wake the patient up after the surgery due to respiratory depression + there's miosis in the eyes (Give Naloxon).

Side effects

- Reversal of analgesia, nausea, vomiting,
- Increased sympathetic nervous system activity: (tachycardia, hypertension, pulmonary edema, and cardiac dysrhythmias).

(g) Dexmedetomidine:

- A sedative agent with analgesic properties. Like benzodiazepines but with the analgesia.
- Highly selective α2-adrenergic receptor agonist.
- A sedated but arousable state similar to natural sleep.
- Weak amnestic; no anticonvulsant properties.
- Airway reflexes remain intact
- Minimal respiratory depression.
- Decreases HR and BP, although transient hypertension may occur after an IV bolus.
- Reduces dose requirements of other anesthetics in GA.
- Used in ICU.
- In microsurgery, we utilize hypotension to decrease blood in visual field.

Pharmacokinetics: Metabolized extensively in the liver.
Adverse effects: Antimuscarinic effects (e.g., dry mouth and blurred vision)

Inhalational Anesthetics

Inhalation anesthetics are usually administered for maintenance of general anesthesia but also can be used for induction, especially in pediatric patients.

-Anesthesia booklet

History of Anesthesia:

- Joseph Priestly – discovers N2O in 1773
- William Morton, dentist – first demonstration of successful surgical anesthesia with ether 1846
- Dr. John Snow administers chloroform to Queen Victoria (1853)– popularizes anesthesia for childbirth in UK
- He becomes the first anesthesia specialist.

Ether and chloroform are explosive and might cause a fire in the OR.
They cause a delayed onset and recovery.

Characteristics of the ideal inhaled anesthetic agent:

- Ample potency,
- Low solubility in blood and tissues, causes rapid onset, rapid recovery.
- Resistance to physical and metabolic degradation,
- Lack of injury to vital tissues.
- The lack of seizures, respiratory irritation, and circulatory stimulation;
- A low cost.
- Allowing the use of a high concentration of oxygen.

The minimum alveolar concentration (MAC)

Halothane, isoflurane, sevoflurane, and desflurane are 0.75%, 1.15%, 1.85%, and 6.0% at one atmosphere

MAC is the volume percentage which allows 50% of the patients to stop responding to painful stimulation. So the MAC is different in every inhalation anesthetic.

Volatile anesthetics

- Present as liquids at room temperature and pressure
- Vaporized into gases for administration

The vaporizer contains the drug in liquid form and each inhalational drug has its own vaporizer because of its unique physical properties.
It's not possible to activate two vaporizers at the same time.

General pharmacokinetics

- The higher the vapor pressure, the more volatile the anesthetic.
- Blood solubility determines the speed of build-up / elimination from blood / brain
- Lower blood solubility means (faster induction/recovery)

Inspired air → Alveolar air → Blood → Brain

Nitrous Oxide

Some hospitals don't use it because of its side effects and it can be replaced by opioids.
It's given with O_2 (ex. 50% N_2O 50% O_2 or 70% N_2O 30% O_2) the minimum of O_2 is 30% and if it becomes less there'll be an automatic shut down of N_2O in modern anesthetic machines to prevent hypoxia.
MAC is 104% at one atmosphere

- **CNS**

Mechanism: antagonism of NMDA receptors in CNS.
- Weak anesthetic, produce analgesia
- Usually combined with other anesthetics. Because it's only an analgesic.
- Used alone e.g. dental procedures);

- **Cardiovascular system**
  - Mild myocardial depressant & a mild sympathetic stimulant.
  - HR and BP are usually unchanged.
  - ↑ pulmonary vascular resistance.
- **Respiratory system.** Little effect on respiration
- **Nausea/vomiting**;
- **Risk of bone marrow depression** with prolonged use.
- **Inhibits vitamin B-12 metabolism**

Expansion of closed gas spaces. nitrous oxide is 35 times more soluble in blood than nitrogen, So the amount of nitrous oxide diffusing into closed air spaces will be greater than the amount of nitrogen diffusing out causing an expansion.

Contraindicated in (e.g. air embolus, pneumothorax increases the size of the pneumothorax, Middle Ear Surgery Causes graft displacement because of middle ear space expansion. Thus, N_2O should be shut off 15 minutes before putting the graft etc.)

Diffuse into the cuff of ETT. ETT: Endotracheal tube.

- **Diffusion hypoxia.** After discontinuation, its rapid elimination from the blood into the lung may lead to a low partial pressure of oxygen in the alveoli. At the end of the surgery we increase the O_2 to 100% to prevent hypoxia.

Volatile anesthetics

Mechanism: Various ion channels in the CNS involved in synaptic transmission (including $GABA_A$, glycine, and glutamate receptors) may play a role.

Metabolism: hepatic.

Exhalation: This is the predominant route of elimination:

- **CNS**
  - Unconsciousness and amnesia.
  - ↑ cerebral blood flow (CBF).
- **Cardiovascular system**
  - Myocardial depression and systemic vasodilation. So try to decrease it as much as possible in open heart surgeries.
  - HR tends to be unchanged, except Desflurane causes tachycardia at the beginning of use or if we increase its MAC.
  - Sensitize the myocardium to the arrhythmogenic effects of catecholamines. (Halothane and isoflurate)

In Septoplasty, epinephrine is added to the local anesthetics to cause vasoconstriction to decrease bleeding and prolong the duration of action.
If the patient is given halothane it can cause arrhythmia because Halothane increases the sensitivity to myocardial arrhythmogenic effect of epinephrine (Halothane and isoflurate augment the effects of epinephrine).
Avoid using Halothane in **Pheochromocytoma**.

- **Neuromuscular system**
  - Dose-dependent ↓ in skeletal muscle tone. Helps the muscle relaxant.

May precipitate malignant hyperthermia. Inhalational Anesthetics and Succinylcholine.
Instead of Inhalational you can give IV Propofol for induction and maintenance, or you can give Spinal or epidural instead of general.

a dramatic increase in body temperature, acidosis, electrolyte imbalance and shock.

- **Hepatic system:** ↓ hepatic perfusion. Rarely, **("halothane hepatitis").** **Prolonged and repeated use of halothane.**
- **Renal system.** ↓ renal blood flow.
- **Respiratory system**
  - Dose-dependent respiratory depression
  - **Airway irritation** and, during light levels of anesthesia, may precipitate coughing, laryngospasm, or bronchospasm

(sevoflurane makes it more suitable) MCQ: Sevoflurane used for induction in children and when they sleep you can switch to IV.

  - **Bronchodilator**,

(with the **exception of desflurane**).

  - Inhibit hypoxic pulmonary vasoconstriction.

Desflurane

Advantages:

- Rapid onset and recovery of anesthesia
- (outpatient procedures)
- One of least metabolized to toxic byproducts.

Disadvantages:

- Requires a special vaporizer
- **Pungent and irritating** to the airway (leading to more coughing, laryngospasm) can't be used for induction.
- High inspired gas concentrations lead to a significant ↑ in the patient's BP & HR.

Sevoflurane

Most commonly used.

Advantages:

- Low solubility in blood-- produces rapid induction and emergence.
- **Pleasant smelling (suitable for children).**
- Has good **bronchodilating** properties.
- Agent of choice in asthma, bronchitis, and COPD.
- It has little effect on the heart rate.
- Mild respiratory and cardiac suppression.

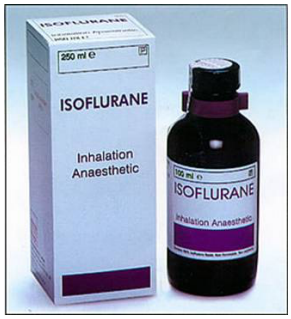
Disadvantages:

- Carbon dioxide absorbents in anesthesia machines degrade sevoflurane to **Compound A**

Isoflurane

Advantages:

- It causes peripheral vasodilation and increased coronary blood flow.

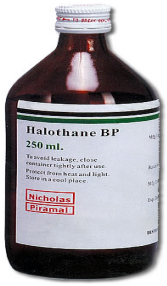


Disadvantages:

- Moderate solubility, so recovery from anesthesia may be delayed.
- Isoflurane can make the heart "more sensitive" to circulating catecholamines (like epinephrine).

Halothane

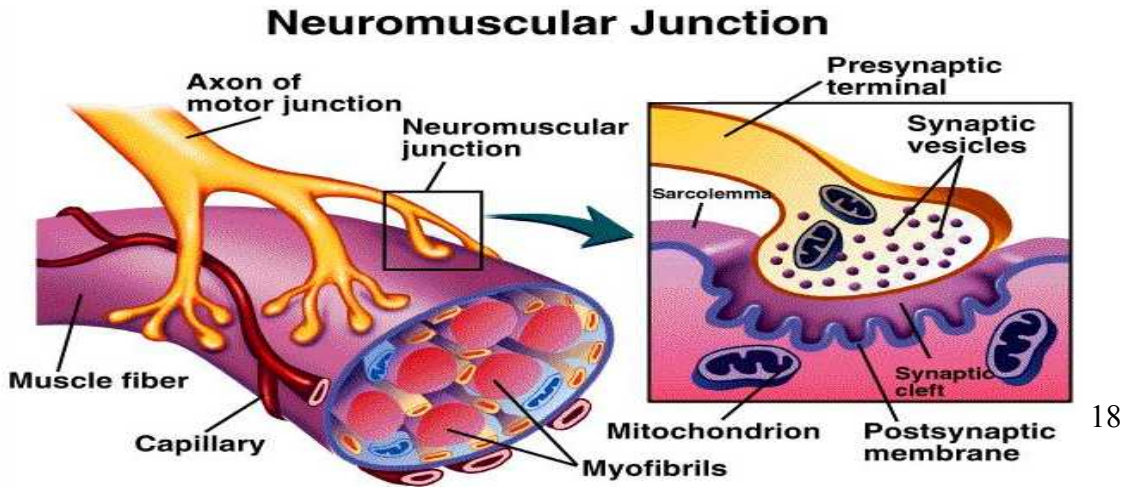
- Oldest one and isn't used anymore.
- Used for induction in children (sweet pleasant odor);
- **Sensitize** the myocardium to the arrhythmogenic effects of catecholamines.
- Blood pressure usually falls.
- Very soluble in blood and adipose
- Prolonged emergence
- "**Halothane hepatitis**" (rare).



Neuromuscular blocking drugs

The principal pharmacologic effect of neuromuscular blocking drugs (NMBDs) is to interrupt transmission of synaptic signaling at the neuromuscular junction (NMJ) by antagonism of the nicotinic acetylcholine receptor (AChR).

-Anesthesia booklet



Neuromuscular blocking drugs are used to:

- Perform tracheal intubation, to prevent causing trauma to the vocal cords.
- Facilitate ventilation, If the patient is breathing he'll antagonize the ventilator so we give muscle relaxants so the breathing will be synchronized with the machine.
- Provide optimal surgical operating conditions**.** Used in abdominal surgeries to decrease abdominal pressure.

Table 9–1. Depolarizing and nondepolarizing muscle relaxants.

Depolarizing	Nondepolarizing
Short-acting	Short-acting
Succinylcholine	Mivacurium
	Intermediate-acting
	Atracurium
	Cisatracurium
	Vecuronium
	Rocuronium
	Long-acting
	Doxacurium
	Pancuronium
	Pipecuronium

All NMBDs are antagonists of the AChR. Each is designated depolarizing or nondepolarizing based on whether it induces a depolarization of the muscle membrane after binding to the receptor. The agents differ substantially in their onset, duration of blockade, metabolism, side effects, and interactions with other drugs.

Succinylcholine (SCh) is currently the only available depolarizing NMBD.

Nondepolarizing NMBDs are often divided by chemical class: aminosteroid derivatives (e.g., pancuronium, vecuronium, and rocuronium) and benzylisoquinolines (e.g., d-tubocurarine, cisatracurium, and mivacurium). The NMBDs also are commonly classified by duration of effect: ultrashort (SCh), short (mivacurium), intermediate (vecuronium, rocuronium, cisatracurium), and long (pancuronium, d-tubocurarine).

-Anesthesia booklet

Neuromuscular blockers:

Depolarizing (Succinycholine)

- Structurally similar to acetylcholine … activate the acetylcholine receptors (Ach) → depolarization of postjunctional membrane.
- Very short duration of action
- A short time intubation (**Rapid sequence induction**) Used in trauma patients and patients with a full stomach or difficult intubation.
  If you have to give general anesthesia to a patient with a full stomach you should give them Succinylcholine because it has a rapid onset which allows you to intubate fast to prevent vomiting or aspiration and it has a short duration, so in difficult intubation the patient will be able to wake up and breathe on his own within 5 minutes.
- Metabolized very quickly by **plasma cholinesterase**.

Characterized by

- Transient muscle fasciculations followed by relaxation.
- Acetylcholine esterase (AChE) inhibitors potentiate rather than reverse the block.

Depolarizing blockade from SCh ends when the molecule diffuses away from the receptor and is broken down to choline and succinic acid in the plasma. SCh is hydrolyzed by plasma cholinesterase (also called butyrylcholinesterase or pseudocholinesterase) to choline and succinic acid. This enzyme is not the same as AChE and is not found in the synaptic cleft. Inhibitors of AchE tend to affect both enzymes, however.

Recovery from SCh-induced depolarizing blockade usually occurs in 10 to 15 min.

-Anesthesia booklet

Side effects of Succinycholine:

- Myalgia: abdomen, back, and neck due to fasciculations.
- **Cardiac dysrhythmias. sinus bradycardia**, junctional rhythm, and even asystole after the first dose in children and following repeated dose within a short time interval in adults. Should give atropine with repeated doses.

- ** **Hyperkalemia** might cause cardiac arrest and shouldn't be used in patients with the following conditions:
  - Major burns,
  - Massive tissue injuries,
  - Extensive denervation of skeletal muscle,
  - upper motor neuron diseases.
- **A transient increase in intraocular pressure.** due to fascicular contractions of the extraocular muscles.
- **Increased intragastric pressure.** results from fasciculation of abdominal muscles.
- **Increase in intracranial pressure.**
- **Succinycholine apnea (Prolonged blockade)**: Patient doesn't wake up due to:
  - Low levels of plasma cholinesterase as in severe liver or kidney disease,
  - A drug-induced inhibition of its activity,
  - A genetically atypical enzyme.

  So we keep the patient on a ventilator for as long as needed.
- Anaphylaxis. over 50% of anaphylactic reactions to NMBDs.
- Malignant hyperthermia (MH).

Nondepolarizing blockers

- They act by competitively blocking the binding of ACh to its receptors and inhibit muscular contraction.
- It is characterized by:
- Absence of fasciculations.
- Potentiation by other nondepolarizing NMBDs and volatile anesthetic agents.
- Reversal by AChE inhibitors.

Mivacurium

- Short-acting.
- Rapidly hydrolyzed by plasma cholinesterase.
- Histamine release causing a transient hypotension and tachycardia.
- Used with caution in patients with known atypical plasma cholinesterase activity or using cholinesterase inhibitors.

Atracurium besylate (Tracrium)

- **Widely used and have an intermediate onset and duration of action.**

- **Histamine release,**
- **No direct cardiovascular effects.**
- Metabolism is by Hofmann degradation and ester **hydrolysis** in the plasma, doesn't depend on the liver or kidneys for metabolism.
- Its duration of action is independent of renal and hepatic function.
- A breakdown product of atracurium, **(laudanosine)** may accumulate and cause seizures.

Cisatracurium (Nimbex)

- Isomer of atracurium
- **Hofmann degradation** and does not accumulate in renal failure. The best choice in patients with renal or hepatic problems.
- Relatively **slow onset** of action.
- Not **release histamine.** Very helpful for patients with bronchial asthma.
- Less **laudanosine**.

Vecuronium bromide (Norcuron)

- Vecuronium is structurally similar to pancuronium but has a slightly faster onset and shorter **(intermediate)** duration of action.
- Not **release histamine**
- No **cardiovascular effects.**
- Metabolism in the **liver** into active metabolites before being excreted in the bile and urine.
- Prolonged clinical effect in elderly patients and those with liver or renal disease.

Rocuronium

- An analog of vecuronium.
- **The most rapid onset** of the clinically available non-depolarizing NMBDs.
- Intubating conditions can be achieved in **60-90 seconds** after an induction dose of 0.6 mg/Kg.
- Increasing the dose to 1.2 mg/kg shortens the time.
- Used when **a rapid sequence induction** is required but SCh is contraindicated. We can use it for RSI instead of SCh by:
  1) Increasing the dose to cause rapid onset of action.
  2) Administering Sugammadex to cause rapid recovery.
  Sugammadex is very expensive and can cause an allergic reaction.
- An intermediate duration of action.

- Metabolized in the liver and excreted in the bile and renal.
- In renal failure ------in a longer duration of action
- **Not release histamine**
- **No cardiovascular effects.**
- Higher incidence of anaphylactic reactions

Pancuronium bromide (Pavulon)

- The first steroid NMBD in clinical use has a slow onset and **long duration** of action. Used for long surgeries
- **No histamine release**
- Weak sympathomimetic properties and causes **tachycardia.** Not used in patients with IHD.
- It is partly metabolized in the liver to a metabolite with neuromuscular blocking properties, and partly excreted unchanged in the urine. Not used in patients with hepatic diseases.
- Its action is prolonged in renal and hepatic impairment.

Long acting NMBDs are associated with post operative pulmonary complications so it's not used a lot anymore. intermediate acting is preferred.

⇒ Patient with Renal/Hepatic disease → use Cisatracurium. If not available, use Atracurium.

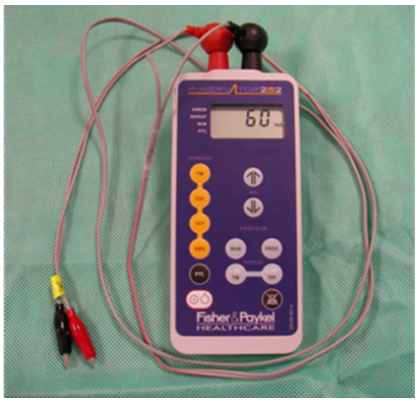
⇒ Rocuronium is a replacement for SCh.

Clinical Choice of NMBD

- **Urgency** for tracheal intubation, incase of full stomach or difficult intubation use SCh. If contraindicated use Rocuronium ONLY IF Sugammadex is available.
- **Duration** of the procedure,
- **Coexisting medical conditions** that may affect the NMJ,
  If Muscle disease → Decrease the dose. If given a full dose the patient won't wake up and he'll need a ventilator.
  If Cardiovascular disease → Vecuronium,
  If Renal disease → Cisatracurium
- **Side effects**
- **Metabolism**
- **Cost-effectiveness**
- **SCh** makes it a good choice for rapid intubation.
- **Rocuronium** will decrease the risk of **hyperkalemia** in patients with burns.

- **Pancuronium** can produce a tachycardia that is undesirable in patients with severe IHD, but its vagolytic effects may be appropriate in pediatrics.

Peripheral nerve stimulator



- Check the depth of neuromuscular blockade.
- Determine that neuromuscular blockade is reversed.
- At least **3 twitches** on a train of four should be detected before attempting reversal.
- To monitor if the patient is relaxed or if he needs a supplemental dose of muscle relaxant.
- After you give Sch you have to check if its effect is gone (patient can breathe again or can move his fingers) before you give nondepolarizing muscle relaxants.

- There are several reasons to monitor neuromuscular function under anesthesia:
  - To facilitate timing of intubation.
  - To provide an objective measurement of relaxation during surgery and degree of recovery before extubation.
  - To titrate dosage according to patient response.
  - To monitor for the development of phase II block.
  - To permit early recognition of patients with abnormal plasma cholinesterase activity.
- Peripheral nerve stimulators use various patterns of stimulation: single-twitch, tetanus, TOF (Train of four).

-Anesthesia booklet

Anticholinesterases (Neostigmine)

- (acetylcholinesterase inhibitors) are agents that inhibit the action of the acetylcholinesterase enzyme at the neuromuscular junction. (Increases concentration of Ach at NMJ)
- Clinical tests of adequate resolution of
- neuromuscular block includes the ability to lift the head from the bed for 5 seconds,
- No role for anticholinesterases in reversing the effects of suxamethonium.

Side effects

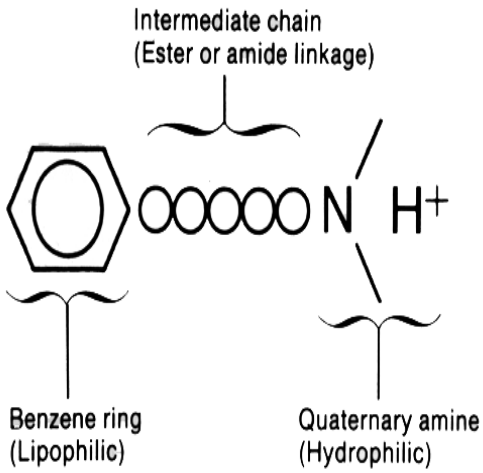
- Bradycardia combine with atropine or glycopyrrolate to prevent it, miosis, GI upset,
- Nausea, bronchospasm, increased bronchial secretions, sweating and salivation.
- For this reason, an antimuscarinic such as glycopyrronium 0.01 mg/kg or atropine 0.02 mg/kg must be administered along with the anticholinesterase to minimise these effects.
- **Intravenous injection at a dose** of 0.05 mg/kg (maximum 5mg).

Local anesthetics (LAs)

LAs are drugs which reversibly prevent the transmission of pain stimuli locally at their site of administration.
Mechanism: reversibly blocking sodium channels to prevent depolarization
Lipid solubility: potency, plasma protein binding determines, duration of action of local anesthetics.

Addition of vasoconstrictor:

- Prolongation of anesthetic action
- Decreased risk of toxicity
- Decrease in bleeding from surgical manipulation.



1. Esters (metabolized by plasma cholinesterase)

- **Cocaine (out of date)**
- **Benzocaine**
- **Procaine**
- **Tertracaine**

2. Amides (metabolized by cytochrome p-450)

- **Lidocaine**
- **Bupivacaine**
- **Mepivacaine**
- **Prilocaine**
- **Ropivacaine**

Applications of local anesthesia:

- **Nerve block**: (e.g., dental and other minor surgical procedures)
- **Topical application**: to skin for analgesia (e.g., benzocaine) or mucous membranes (for diagnostic procedures) Ex. In children so IV insertion won't hurt.
- **Spinal & epidural anesthesia**
- **Local infiltration**: at end of surgery to produce long-lasting post-surgical analgesia (reduces need for narcotics)
- **I.V. infusion**: for control of cardiac arrhythmias (e.g., lidocaine for ventricular arrhythmias)

LAs are very toxic if given Intravenously except Lidocaine. It's the only LA administered Intravenously as an antiarrhythmic.

Choice of local anesthetics

- Onset
- Duration
- Sensory vs. motor block
- Potential for toxicity

Lidocaine

- Amide type anesthetic
- Lidocaine was introduced in 1948
- The most commonly used local anesthetic
- **Rapid onset** and a duration of 60-75 minutes
- Extended with epinephrine for up to 2 hours
- Metabolized in the liver and excreted by the kidneys.
- Contraindicated in patients with a known sensitivity to amide type anesthetics
- Has also **antiarrhythmic** action.

Bupivacaine

- Amide-type local anesthetic
- Introduced in 1963
- Onset of action is **slower** than lidocaine and anesthesia is **long acting**.
- Provides 2-4 hours of anesthesia
- Extended with epinephrine for up to 7 hours
- **More cardio-toxic** than lidocaine, difficult to treat.

While doing a brachial plexus block you may inject it intravascularly by mistake. So you should always aspirate before injecting.

Bupivacaine induced cardiac toxicity is treated with Intralipid.

- Metabolized in the liver and excreted by the kidneys
- Contraindication: known hypersensitivity

You can combine the two drugs to take advantage of Lidocaine's rapid onset, and Bupivacaine's long duration of action.

Ropivacaine

- A less toxic, **long-lasting LA**.
- Undergoes extensive hepatic metabolism, with only 1% of the drug eliminated unchanged in the urine.
- Ropivacaine is slightly **less potent** than bupivacaine.

Local Anesthetic Toxicity

- **Central nervous system**
- **Initially** → **circumoral numbness**, dizziness, tinnitus, visual change.

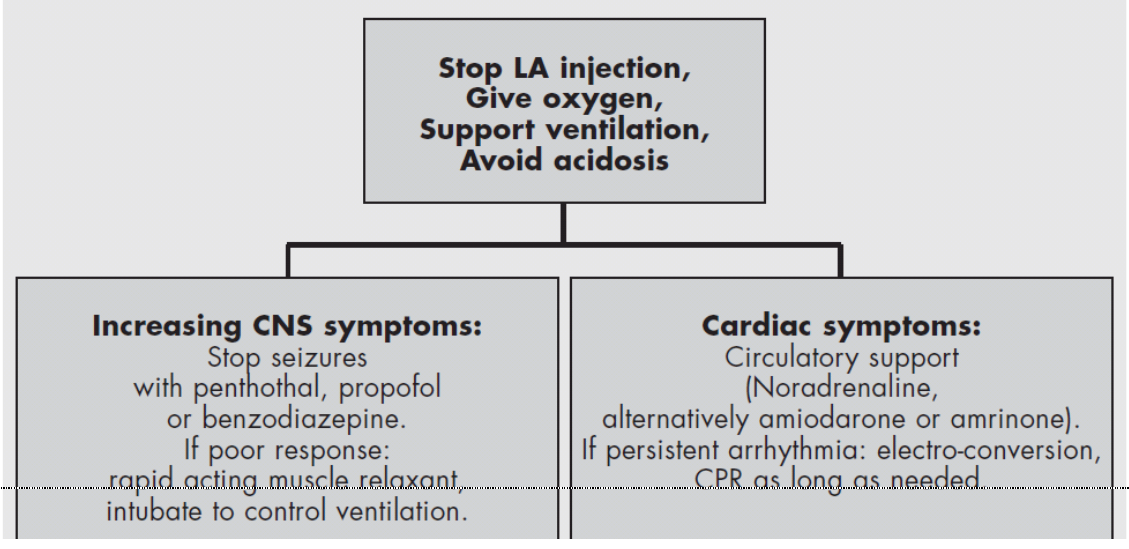
First sign is circumoral numbness.

- **Later** → drowsiness, disorientation, slurred speech, loss of consciousness, convulsions.
- **Finally** → respiratory depression.
- **Cardiovascular**: Myocardial depression and vasodilation--hypotension and circulatory collapse.
- **Allergic reactions** → rare (less than 1%).
- preservatives or metabolites of esters.
- rash, bronchospasm.

Prevention and Treatment of Toxicity

All cases:

Treatment of local anaesthetic intoxication



Case 1: (adult)

- 18 y for septoplasty
- Routine pre-operative evaluation and laboratory studies according to the hospital's standard.
- Fasted overnight.
- **Premedication**: **midazolam** 0.05 mg/kg and ranitidine 150 mg orally 2 h pre. Premedication doesn't always have to be a sedative.
- **Induction** : **propofol** 2–3 mg/kg IV, **fentanyl** 2 ug/kg IV and **cisatrachrium** (0.15 mg/kg) IV. We didn't give SCh because its an elective (patient is fasting).
- **Maintenance:** 50% oxygen in air and 1.5–2% **sevoflurane**. You can use desflurane or isoflurane.
- Neuromuscular blockade was maintained by administering intermittent boluses of cisatracurium if needed. Guided by nerve stimulator or clinically by return of breathing etc.
- Patients were mechanically ventilated to maintain ETCO2 (35–40 mmHg). **End-tidal CO2**
- During surgery, the surgeon infiltrate the operative site by 1% lidocaine with epinephrine (1:100,000) for bleeding and pain control.
- At the end of the surgery, anesthesia was discontinued and 100% oxygen was administered.
- The oral cavity was inspected, throat pack was removed and then the secretions and blood clots were aspirated.
- **Reversal: neostigmine** 40 ug/kg and atropine 20 ug/kg i.v. we start the reversal if the nerve stimulator was 3/4 or the patient started breathing or moving his fingers.
- **Extubation:** awake after the return of protective airway reflexes.

Case 2: (child)

- 3 y old child for adenotonsillectomy.
- Fasted 6 h for solid food, but clear fluids were given for up to 4 h
- **Premedication:** 0.3 mg/kg oral **midazolam** 30 min before induction.
- **Induction: sevoflurane** in 100% oxygen (6 L/min) through a facemask increase it gradually until he's unconscious then establish iv access.
- An IV-cannula was established,
- **Fentanyl** (2 µg/kg IV) + **Rocuronium** 0.6 mg/kg.
- **Maintenance:** O_2 in nitrous oxide 50% and **sevoflurane** at 2-3 vol %.
- Adjusted to maintain adequate anesthesia and stable hemodynamics. If BP and PR are stable it's a sign that he's sleeping but if he starts to sweat or his eyes tear, it's a sign of light anesthesia.
- Bispectral index can be used to monitor the depth of anesthesia by inspecting the patient's EEG.
- Lung ventilation was controlled to maintain ETco2 (30 and 35 mmHg).
- At the end of surgery, once hemostasis was achieved, the inhalational anesthetics were discontinued,
- **Reversal: Prostigmine & glycopyrrolate**

Summary

- **Inhalation anesthetics** are usually administered for maintenance of general anesthesia but also can be used for induction, especially in pediatric patients.
- Low solubility of Inhalation anesthetics in blood and tissues, causes rapid onset, rapid recovery.
- **Nitrous Oxide** can cause Expansion of closed gas spaces thus it's Contraindicated in (e.g. air embolus, pneumothorax and Middle Ear Surgery etc.).
- Avoid using **Halothane** and **Isoflurane** in cases of increased chatecholamines (ex. Pheochromocytoma).
- **Inhalational Anesthesia (IA)** and **Succinylcholine** may precipitate malignant hyperthermia.
- Prolonged and repeated use of **halothane** can cause halothane hepatitis (rare).
- IAs have a Bronchodilator effect with the exception of **Desflurane**.
- **Desflurane** has Rapid onset and recovery of anesthesia but it's Pungent and irritating to the airway.
- **Desflurane** causes tachycardia at the beginning of use or if we increase its MAC.
- **Sevoflurane** is Pleasant smelling, so it's suitable for children.
- **Neuromuscular blocking drugs** are used to Perform tracheal intubation, facilitate ventilation, and provide optimal surgical operating conditions.
- **Succinylcholine** has a Very short duration of action and recovery from SCh-induced depolarizing blockade usually occurs in 10 to 15 min so its very suitable for Rapid sequence induction (Used in trauma patients and patients with a full stomach or difficult intubation).
- Side effects of **Succinycholine** include Cardiac dysrhythmias, sinus bradycardia and Hyperkalemia.
- **Atracurium besylate** causes Histamine release, has no direct cardiovascular effects and is metabolized by Hofmann degradation and ester hydrolysis in the plasma.
- A breakdown product of **Atracurium**, **(laudanosine)** may accumulate and cause seizures.
- **Cisatracurium** is metabolized by Hofmann degradation and doesn't cause Histamine release.
- **Vecuronium bromide** doesn't cause histamine release, has no cardiovascular effects and is metabolized in the liver and has a prolonged clinical effect in elderly patients and those with liver or renal disease.
- **Rocuronium** has the most rapid onset of the clinically available non-depolarizing NMBDs and is used when a rapid sequence induction is required but SCh is contraindicated. It doesn't cause histamine release and has no cardiovascular effects.

- **Pancuronium bromide** is used for long surgeries and doesn't cause histamine release.
- Patient with Renal/Hepatic disease → use **Cisatracurium**. If not available, use **Atracurium**.
- Clinical Choice of NMBD is affected by Coexisting medical conditions that may affect the NMJ, such as:
    - If Muscle disease is present → Decrease the dose. If given a full dose the patient won't wake up and he'll need a ventilator.
    - If Cardiovascular disease is present → **Vecuronium**,
    - If Renal disease is present → **Cisatracurium**
- At least 3 twitches on a train of four in a peripheral nerve stimulator should be detected before attempting reversal.
- **Acetylcholinesterase inhibitors** (ex. **Neostigmine**) are agents that inhibit the action of the acetylcholinesterase enzyme at the neuromuscular junction. (Increases concentration of Ach at NMJ)
- **Neostigmine** can be combined with **atropine** or **glycopyrrolate** to prevent Bradycardia.
- LAs are very toxic if given Intravenously except **Lidocaine**. It's the only LA administered Intravenously as an antiarrhythmic.
- **Bupivacaine** is more cardio-toxic than lidocaine and difficult to treat.
- First sign of local anesthetic toxicity is circumoral numbness.
- Prevention and treatment of toxicity:

All cases:
assure adequate ventilation
administer supplemental oxygen

Seizures:
diazepam (Valium)

Hypotension
Trendelenburg position (head down, legs up)
IV fluid bolus (isotonic saline or LR)
vasopressors (dopamine) (if refractory to above)

Dysrhythmias
as per ACLS protocol (but do not administer further lidocaine)

MCQ's:

1) A 74-year-old woman with a history of a previous total abdominal hysterectomy presents with abdominal pain and distention for 3 days. She is noted on plain films to have dilated small-bowel and air-fluid levels. She is taken to the operating room for a small-bowel obstruction. Which of the following inhalational anesthetics should be avoided because of accumulation in air-filled cavities during general anesthesia?
a. Diethyl ether
b. Nitrous oxide
c. Halothane
d. Methoxyflurane
e. Trichloroethylene

The answer is b. (Townsend, p 432.) Nitrous oxide has a low solubility compared with other inhalation anesthetics; nitrous oxide is more soluble in blood than nitrogen and is the only anesthetic gas less dense than air. As a result of these properties, nitrous oxide may cause progressive distension of air-filled spaces during prolonged anesthesia. Since nitrous oxide diffuses into gas-filled compartments faster than nitrogen can diffuse out, its use can lead to worsened distention, which may be undesirable (eg, in an operation for intestinal obstruction).

2) A 30-year-old man is scheduled for a laparoscopic cholecystectomy for biliary colic. He reports a family history of prolonged paralysis during general anesthesia. Which of the following medications should be avoided during his procedure?
a. Succinylcholine
b. Vecuronium
c. Pancuronium
d. Halothane
e. Etomidate

The answer is a. (Brunicardi, pp 1734-1739.) The family history is suggestive of a pseudocholinesterase deficiency which prolongs the effects of succinylcholine, a depolarizing neuromuscular blocking agent,

as well as of mivacurium, a non-depolarizing agent. Vecuronium, pancuronium, and cis-atracurium are other nondepolarizing agents that are not affected by this enzyme deficiency. Etomidate is used for rapid sequence induction and is not affected by pseudocholinesterase deficiency; etomidate does block steroid synthesis and has been associated with acute adrenal insufficiency, but the clinical relevance of the resultant insufficiency is controversial.