# Pharmacology of General Anesthetics


Done by: Dina Assiri
Fatema Abdulkarim

Team Leader: Nada Al-Madhi

From slides | Doctor's Notes | Team's Notes | From the book | Important

# Table of Contents

**This introduction was mentioned by the Dr., and is not in the slides:**

General anesthesia is composed of 4 elements:
Loss of consciousness - Analgesia - Amnesia - Muscle relaxation.

NOT ALL DRUGS give all these 4 effects so we cannot depend on one drug only. We can use many drugs together to fulfill the target of general anesthesia . Patient must be on muscle relaxants to prevent movement in certain situations such as: during intubation - abdominal surgeries for the retraction of abdominal wall - neurosurgeries like intracranial surgeries.

IMP
During surgery, there is autonomic stimulation due to pain so we expect activation of the sympathetic system ( tachycardia, HTN) due the release of catecholamines. Therefore, when selecting a drug for GA , we need to make sure this drug doesn't cause sympathetic stimulation ( tachycardia, HTN) nor severe hypotension that leads to myocardial depression and decreased CO.

If a drug is metabolized by the liver and it were diseased for any reason , the drug effect will be prolonged ; the same happens with the kidneys in case of renal failure.

Definitions:
Pharmacokinetics: What our bodies do to the drug ?
(metabolism by transformation, excretion and elimination of the drug)
Pharmacodynamics: The effect of the drug on our bodies ( on the CNS, CVS ..)

Anesthesia for any surgery is done by :
1. INDUCTION: START of anesthesia . We either use IV , IM or inhalation which is more suitable and more commonly used for children and can be used for adults as well . Children don't like IV and will start crying..
2. Induction has to be followed by MAINTENANCE: This is mostly by inhalation anesthetics or total IV with some drugs like Propofol.
3. EMERGENCE: or ” How to wake the patient up ? “
   Some patients have a delayed recovery due to a drug that causes this delay. However, if the drug has a rapid recovery , we’ll have a fast emergence . Emergence has to be fast cause most surgeries nowadays are outpatient ( day case) surgeries to reduce the costs by reducing the patient’s stay . What made us start the day case surgeries is the recently made anesthetic medications that cause rasped induction and recovery.

Premedication : any patient coming for surgery will be anxious so we give sedative drugs the night before surgery or at the holding area for children .
ex: Patient with IHD comes in for surgery , he will be anxious with an increase in catecholeamines and tachycardia which is dangerous for IHD so we give meds ..

**LECTURE STARTS HERE:**

# Intravenous Anaesthetics

## 1.Benzodiazepines (BZ)

- Include *midazolam (advertised as dormicum)*, *lorazepam*, and *diazepam(advertised as valium)*.
- **Primary uses:** sedation, amnesia, adjuncts to general anesthesia, or in anxiolysis for premedication give a tablet of midazolam, lorazepam or diazepam during induction of anesthesia. We can use a midozolam then complete it with another drug but we can't use midazolam alone for induction of anesthesia! (WHY?) **MIDAZOLAM** is mainly a **SEDATIVE**. Example: If patient comes with abscess and needs incision and drainage and you give him ***MIDAZOLAM***, he will ***SLEEP*** but will ***JUMP*** when you touch him cause it has ***NO ANALGESIC EFFECT*** .
- **Mechanism:** enhance inhibitory neurotransmission by increasing the affinity of GABAA receptors for GABA.
- **Pharmacokinetics:**
  - **Effects are terminated by redistribution:** so they have a short duration of action . Midazolam has the shortest followed by diazepam then lorazepam with half lives of 2 , 11, and 20 hours respectively.
  - **All three drugs are metabolized in the liver:** so incase of liver disease they'll have a prolonged duration of action.
  - **Diazepam clearance is reduced in the elderly, but this is less of a problem with midazolam and lorazepam:** In old age, we have slow metabolism of drugs cause function worsens with aging . Therefore, there is prolongation in the duration of any drug metabolized in the liver in elderly .

- **Pharmacodynamics:**
  - A. **CNS**
    - Amnestic, anticonvulsant, anxiolytic, muscle-relaxant, and sedative-hypnotic effects in a dose-dependent manner. Higher dose means more sedation.
    - Do not produce significant analgesia. NO analgesia effect AT ALL.
  - B. **Cardiovascular system**
    - Mild systemic vasodilation and decrease in cardiac output. HR is usually unchanged. But decreasing the degree of hypotension isn't too much in this group.
  - C. **Respiratory system**
    - Mild dose-dependent decreases in RR and TV.
    - Respiratory depression may be pronounced if administered with an opioid. Benzodiazepines cause little respiratory depression but if used with opioids more respiratory depression will be pronounced.

- **Adverse effects :**

  A. **Drug interactions**

  - Patient receiving the anticonvulsant valproate may precipitate a psychotic episode. With diazepam.

  B. **Pregnancy and labor**

  - Risk of cleft lip and palate when administered during the first trimester. Better to avoid those drugs in pregnancy cause it increases the risk of congenital anomalies. Also, in C/S it might pass through the placenta and cause respiratory depression in neonates after delivery.

  C. **Superficial thrombophlebitis and injection pain** by diazepam (especially) and lorazepam but NOT with *midazolam* .

- **Advantages:**
  - Amnesia
  - Relatively little cardiovascular effect
  - Anti-convulsant

- **Disadvantages:**
  - No analgesic effect
  - Causes Respiratory depression with large doses
  - Long acting ( diazepam or repeated injections of midazolam ) repeated IV doses or infusion of such drugs.

Sometimes we use sedation ONLY not GA like in MRI . For example, a child that comes for MRI . Sedation can have various degrees from mild to moderate. Every time you increase the dose of drug, you increase the level of sedation . If we increase the dose LARGELY, we can reach the level of anesthesia.

**What is the difference between sedation and Anesthesia?**

During sedation, patient is sleeping and can maintain his airway to a certain point and breathe comfortably . However, with increasing sedation, patient enters deep sleep and the tongue falls back causing airway obstruction and respiratory depression. So with increasing the dose for sedation pay attention to the airway and respiration cause patient might develop airway obstruction for when under GA airway obstruction may happen.

**THE THREE TYPES OF BENZODIAZEPINES ARE:**

C. ***Diazepam*** *(Valium)*
It is water-insoluble, so IV use can cause local irritation/pain

*D.* ***Midazolam*** *(Dormicum)*

Water soluble, so drug of choice for IV administration It has a more rapid onset and more rapid elimination than the other BZ's. The most potent amnestic . Can be given by many routes (IV, IM, oral, rectal, intranasal)

E. ***Lorazepam*** *(Ativan)*

Water-insoluble, less potent amnestic than midazolam, but a more potent amnestic than diazepam.

****FLUMAZENIL (ANTIDOTE FOR BZ)**

If patient is given sedation and is still sleepy after operation and we want to wake him up, we give FLUMAZENIL. When it's given, the sedative effect will be reduced but will come back again cause it has a short duration of action so REPEAT the dose and observe the patient .

- **A competitive antagonist** at the benzodiazepine binding site of GABAA receptors in the CNS.
  - Reversal sedative effects occurs within 2 minutes; peak effects at 10 minutes.
  - Half-life is shorter than the benzodiazepine.When it's given, the sedative effect will be reduced but will come back again cause flumazenil has a short duration of action so REPEATED DOSES may be needed and observe the patient .
  - Metabolized to inactive metabolites in the liver.
  - **Dose**. 0.3 mg IV every 30 to 60 seconds (to a maximum dose of 5 mg).

## 2. Barbiturates

- Such as *thiopental* and *methohexital*. In our hospital the most commonly used drug is PROPOFOL. Thiopental was used previously (10 years ago) but nowadays propofol is becoming more famous due to its advantages.Thiopental is cheaper.

**Thiopental is used for management of patient with fits and seizures.

- **Mechanism :** barbiturates facilitate inhibitory neurotransmission by enhancing GABAA receptor function. The also inhibit excitatory neurotransmission via glutamate and nicotinic acetylcholine receptors.

- **Primary use:** Induction of anaesthesia

- **Advantages:**

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

- **Pharmacokinetics:**
  - **Hepatic metabolism**.Thiopental is metabolised to pentobarbital, an active metabolite with a longer half-life.
  - Multiple doses or prolonged infusions may produce prolonged sedation or unconsciousness due to accumulation of drug in the body.

**Elimination if this drug is by redistribution. It will reach after IV injection to the brain then will be redistributed to the muscle so its effect will fade away.

- **Pharmacodynamics:**
  A. **CNS**
  – Dose-dependent CNS depression . Dose-dependent cerebral vasoconstriction and decrease in (CMRO2) "cerebral metabolic rate"cause reductions in ICP and (CBF). Most IV anaesthetics reduce ICP **EXCEPT KATAMINE**. Dose-dependent depression of EEG activity.
  **Cardiovascular system**
  – Cause vesodilation and depress myocardial contractility, leading to dose-dependent decreases in BP and cardiac output,
  – Baroreceptor reflexes remain largely intact;

B. **Respiratory System**

– Dose-dependent decreases in RR and TV.

Ventilatory responses to hypoxia and hypercarbia are markedly depressed at the site of chemoreceptors and respiratory centres.

**Apnea** may result for 30 to 90 seconds after an induction dose so when thiopental is given pt. might become apneic due to depression of respiratory centre so airway obstruction might take place .

– **Laryngeal reflexes remain more intact** compared with propofol; therefore, the incidence of cough and laryngospasm is higher.

- **Adverse effects:**

A. **Allergy. (histamine release)**

**Porphyria(stimulate prophyrin enzymes accumulation of toxic heme metabolism) so it is absolutely contraindicated in acute intermittent porphyria**

B. **Venous irritation (esp if extravasated) 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.

C. **Myoclonus and hiccups** ( more with methohexital)

- **Dosage and Administration:**
  - Thiopental for induction IV 3-6 mg/kg; for sedation IV 0.5-1.5 mg/kg
  - *N.B. Reduce doses in hypovolemic: they have an exhausted sympathetic system ( cause those drugs cause myocardial depression and cardiac output so take care in shocked pts for it may cause cardiac arrest) , elderly (due to reduction of liver function), or hemodynamically compromised patients.*

- ***Disad*vantages:**
  - Not analgesic
  - Decrease blood pressure
  - Decrease respiratory rate and tidal volume or apnea.
  - Coughing, laryngospasm, bronchospasm.(due to intact airway reflexes)

## 3.Opioids

- Opioids produce moderate sedation and profound analgesia.(mainly given for analgesia but have also a sedative effect)
- They exert their effects by binding with opioid receptors in CNS ( 3 major opioid receptors **μ** (mu), **κ** (kappa), and **δ** (delta).
- Meperidine(pethedine) (not used so much now and is 10 times less potent than morphine and has a metabolite called normeperidine that causes convulsions so it shouldn't be used in pts with renal failure to prevent the accumulation of this active metabolite), morphine , alfentanil, fentanyl, sufentanil, remifentanil are commonly used.
- **Naloxone** is pure antagonist that reverses analgesia and respiratory depression non-selectively--, effects may recur when metabolized "antidote for opioids so in case of respiratory depression due to opioids, use naloxone "
- **Trick when using naloxone : Suppose we have a pt suffering from respiratory depression due to fentanyl and we gave him naloxone.. What do we expect? We expect that the analgesic effect of fentanyl will be reversed as well so the pt may feel pain immediately for not only respiratory depression effect will be reversed but also it's analgesic effect.
- **ALSO it has a short duration of action so we may need repeated doses or give it by IV infusion to maintain the antagonism of respiratory depression.

- **Advantages:**
  - Profound analgesia
  - Reduces emergence phenomena means when we use sevoflurane ,which is a drug with rapid recovery, sometimes patients "especially children' wake up and are not aware of the surrounding environment so they get agitated .This phenomena is reduced when using fentanyl)
  - Minimal cardiac effects-- no myocardial depression
  - Therefore it's the drug of choice used in open heart surgery (mainly depend on opiods) and also IHD and CHF due to little myocardial depression
  - Bradycardia in large doses
  - Respiratory depression at high doses
  - Some peripheral vasodilation and histamine release – hypotension histamine release more with morphine

- **Side effects:**
  - Nausea and vomiting due to stimulation of chemoreceptors in trigger zone , Drowsiness or sedation, Miosis due to stimulation of chemoreceptor zone , chest wall rigidity (if given fentanyl sometimes you can't ventilate and it will continue for a few mins then disappear), seizures, constipation, urinary retention spasticity of sphincter , Slow gastric emptying ,biliary colic(spasm of biliary tract)
  - Nausea and vomiting distressing postoperatively and respiratory depression are the main complications that we worry about with opioids

- postoperative N/V is seen especially in surgeries like adenomectomy , tempanoplasty, and laparoscopic cholecystectomy and is exaggerated when using opioids

**TYPES of Opioids:**

**A. Fentanyl (most commonly used) 95% 1 milligram=1000 microgram**

A potent synthetic opioid agonist with between 50-100 times the analgesic potency of morphine. One ampule is 100 milligram ; however, morphine ampule is 10 milligram).Regarding the potency of both drugs, 10 microgram of fentanyl is equal to 1 milligram of morphine)This high potency is due to high lipid solubility

Used to aid induction(all patients have it) and maintenance ( cause within 3 hours it'll fade away with time) (give another bolus (intermittent doses) of general anesthesia Eg.during induction give 200 microgram and during surgery give 50 micg then another 50 micg or 25 micg

How do you know that there is a reduction in the effect of fentanyl? When we notice tachycardia and HTN, we know that the analgesic effect has been reduced so the pt needs more analgesia.

To supplement regional and spinal anesthesia and epidural(give prolonged and better effect when used with the local anesthetics in spinal and epidural)

Ability to maintain cardiac stability.

**B. Sufentanil citrate (Sufenta) ☒ not used very much**

✓Sufentanil has been reported to be as much as 10 times as potent as fentanyl

✓ Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with equipotent dosages of fentanyl. "ADVANTAGE"

**C. Alfentanil (NOT COMMONLY USED)**

✓Compared to fentanyl and sufentanil, it has a shorter duration of action because its high protein binding and relatively low lipid solubility . fentanyl.

**D.Remifentanil (Ultiva) recent (new) v. good advantage**

✓Ultra short acting and rapidly cleared cause it doesn't depend on hepatic metabolism

✓IMP: widespread ***extrahepatic*** metabolism by blood and tissue ***nonspecific esterase***, therefore rapidly metabolised and cleared

✓**ART** of remifentanil: Infusion but once stopped immediately effect will go

✓PROBLEMS: 1-Expensive and 2-may cause bradycardia

✓****TRICK** with remifentanil: we should give analgesic(NSAIDS, morphine) after stopping it cause he'll feel pain immediately.

✓Its suitable for outpatient day case surgeon **ADVANTAGE**

**E.Morphine** (old drug and has many side effects)

✓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.

✓Hypotension

✓Spasm of biliary sphincter causing biliary colic, histamine release not a good choice for renal failure can cause sedation because of metabolite: morphine 6 glucuronide accumulation so use with caution!

**4.Ketamine (old drug)**

- A sedative-hypnotic agent with potent analgesic properties even with subanesthetic (small) dose
- Sedative and potent and long time analgesic (shamell)
- Not used nowadays because of propofol but in children can be used

- **Primary uses:**
  - Induction or anaesthesia in patients w/ cardiovascular problems
  - Sedation or general anaesthesia in children Can be given IM IN CHILDREN if afraid of IV

- **Mechanism:** Anaesthetic effects are mainly attributed to noncompetitive antagonism of NMDA receptors in the CNS.
- **Pharmacokinetics:**
  - Produces unconsciousness in 30 to 60 seconds after an IV induction dose.
  - Effects are **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 HAVE SEDATIVE EFFECTS ). Elimination half-life is 2 to 3 hours.

    Repeated bolus doses or prolonged infusions result in accumulation .

- **Pharmacodynamics:**

  A. **CNS**

– Produces a “dissociative” state of CNS accompanied by amnesia and profound analgesia.
– IMP : Increases (CBF), and (ICP) pressure.
– So we never use ketamine in patients with head trauma or brain tumour cause it increases ICP.

  B. **Cardiovascular system**

– Increases HR( MCQ : ketamine causes tachycardia and HTN), COP, and BP by causing the release of endogenous catecholamines.
– MCQ:Used in hemodynamically compromised patients like in pts with shock and hypotension so it will correct the BP due to its hypertensive effect.

  C. **Respiratory system**

– Mild depression of respiratory rate( RR) and tidal volume(TV).
– IMP :Potent bronchodilator (that’s why one of the management of status asthmatics and bronchial asthma )
– Laryngeal protective reflexes are relatively well maintained.movable vocal cords.However, aspiration might still happen if given with a full stomach and no endotracheal tube even if laryngeal reflexes are intact.

- **Dosage and administration:** Induction IV 1-2mg/kg
  IM 3-5mg/kg

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

- **Adverse effects:**
  - **Oral secretions** . Reduce by atropine and glycovirulate
  - **Emotional disturbance.** agitation and unpleasant hallucinations( dreams and they might tell you their secrets) during the early postoperative recovery period. This is seen less in children and more in females with increasing age and high doses => reason why we don't use it too much. **MCQ :HALLUCINATION =KETMAMINE**
  - **Muscle tone:** often increased.
  - **Increases ICP** : contraindicated in patients with head trauma or intracranial hypertension.
  - **Ocular effects.** mydriasis, nystagmus , diplopia, and increased intraocular pressure. **MCQ WE NEVER USE IT IN OPTHALMIC SURGERY !**

- **Advantages:**
  - Cardiovascular stimulant, HTN, Tachycardia
  - Bronchodilator
  - Profound analgesia and amnesia

- **Disadvantages:**
  - Emergence reactions (not in children <15; adults >65)
  - **Increases intracranial pressure**
  - **Hallucination**

## 5.Propofol(Diprivan)


- 1% isotonic oil-in-water emulsion, which contains egg lecithin, glycerol, and soybean oil.
- **Primary uses:**

- A sedative/hypnotic (ICU)
- Induction or maintenance so sometimes it is used as infusion and we call that TIVA total intravenous anesthesia
- The onset begins after 30 s. After a single dose patient recovers after 5 min with a clear head and no hangover
  So it's good for pts with abscess for incision and drainage .
- Facilitates inhibitory neurotransmission by enhancing the function (GABAA) receptors in CNS

- **Pharmacokinetics**

Hepatic and extrahepatic metabolism to inactive metabolites(it has a rapid recovery cause its inactive) which are renally excreted.

- **Pharmacodynamics**

A. **CNS**

- **Induction** : rapid onset of unconsciousness (30 to 45 seconds), followed by a rapid termination of effect due to redistribution.
- Emergence is rapid

  Weak analgesic effects .
- Decreases (ICP) and also (CPP) due to markedly decreased hypotension (MAP).

  Propofol is an anticonvulsant . And antiemetic effect postoperative so TIVA is given during surgery so reduce n/v postop.
- Dose-dependent suppression of (EEG) activity.

  Less (PONV) occurs.

B. **Cardiovascular system**

- Dose-dependent decreases in preload, after load, and contractility lead to decreases in (BP) and cardiac output.
- **Hypotension** may be marked in hypovolemic, elderly, or hemodynamically compromised shocked patients.
- Heart rate (HR) is minimally affected, and baroreceptor reflex is blunted.

C. **Respiratory system**

- Dose-dependent decreases in (RR) and (TV).
- Ventilatory responses to hypoxia and hypercarbia are diminished.

- **Dosage and administration:**
  - Induction IV 1-2.5mg/kg
  - Sedation IV 25-100 µ/kg/min (give small dose infusion for anxious pts coming for surgery to sedate only)
  - Titrate with incremental doses in hypovolemic, elderly, or hemodynamically compromised patients or if administered with other anesthetics to reduce the degree of hypotension. But better to use ketamine if available!
  - Propofol emulsion supports bacterial growth that's why it"s given with antimicrobial agents to prevent this problem . Also use sterile technique when opening the ampule and write the date cause we can only use it within 6 hours and should discard it after that to prevent bacterial growth.

- **Adverse effects:**

- MCQ **Venous irritation. Patient taking propofol fentanyl and succinylcholine and felt some pain during injection ✅ from which drug ✅ PROPOFOL WHEN USED ALONE ✅ CAUSE VENOUS IRRITATION ✅ ADD LIDOCAINE AOR ZILOCAINE WITH PROPOFOL ✅ doctors do that in OR to prevent venous irritation and pain during injection . This is a very famous problem with propofol!**

**- Lipid disorders.** used cautiously in patients with disorders of lipid metabolism (e.g., hyperlipidemia and pancreatitis). Because propofol itself increases the level of lipids especially with LARGE infusion(12 hours, 24 hours) in ICU for sedation

- ***Myoclonus and hiccups*** (can happen with propofol and methahixane but most commonly with **etomodate**

- **Propofol infusion syndrome**
  - A rare when used in ICU mainly for prolonged period (not in OR)
  - 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.

- **Advantages:**
  - Rapid induction and recovery times even after repeated injections
  - Anti-emetic properties IMP

- **Disadvantages:**
  - Pain on injection IMP
  - Respiratory depression ,apnea
  - Bradycardia and hypotension.

**6.Etomidate**

- **Primary use: not commonly used:**

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.
  - Rapid induction and rapid recovery and no analgesic property (like propofol)
  - Very high clearance in the liver and by circulating esterases to inactive metabolites (rapid recovery)

- **Pharmacodynamics:**
  - A. **CNS**
    - No analgesic properties

      Cerebral blood flow (CBF), cerebral metabolic rate, and intracranial pressure decrease
    - Dose-dependent depression of EEG activity,
  - B. **Cardiovascular system**
    - Minimal changes in HR, BP
      Therefore, mainly used in hemodynamic compromised patients (car accident internal hemorrhage given IV fluid waiting for blood and hypotensive) ✗ catecholamines physiological response to maintain BP to keep him alive ✗ best to not change this response by giving a drug that may cause hypotension
    - Can use ketamine ✗ although might use hallucination and also depends on availability.
    - Does not affect the sympathetic tone or the baroreceptor function.
  - C. **Respiratory system less than propofol**
    - Dose-dependent decreases in respiratory rate( RR) and tidal volume(TV); transient apnea may occur.
    - The respiratory depressant effects of etomidate are less pronounced .

- **Dosage and administration:**

Induction IV 0.2-0.5mg/kg

- **Adverse effects:**

- **Myoclonus** (abnormal limb movements) very famous to cause it
- **Nausea and vomiting** .
- **Venous irritation and superficial thrombophlebitis (like propofol)** may be caused by the propylene glycol vehicle. Minimized by administration into a free-flowing IV carrier infusion.
- **Adrenal suppression.**
  - Inhibits 11β-hydroxylase;
  - a single induction dose suppresses adrenal steroid synthesis for up to 24 hours. (but not clinically significant in OR)
  - repeated doses or prolong infusions have been associated with increased mortality in ICU patients cause they are already on steroids and their adrenals are already suppressed
- Intensive care => clinically significant => critically ill and already have damaged function of adrenals

- **Advantages:**
  - Rapid induction rapid recovery
  - Ultra-short acting (5 min)
  - **No cardiovascular depression IMP**
  - Minimal respiratory depression

- **Disadvantages:**
  - Pain on injection
  - Involuntary muscular movement(myoclonus)
  - Nausea and vomiting
  - Hiccups
  - Not analgesic
  - Adrenocortical suppression IMP MCQ

**7. Dexmedetomidine (Precedex):**

- A sedative(like bz agents but with analgesic property) agent with analgesic properties
- Used for adult surgeries not approved for children
- Highly selective α2-adrenergic receptor agonist (like clonidine but more selective with less side effects) .
- Metabolized extensively in the liver
- What makes its special when compared to medazolam ?? A sedated but ***arousable*** state similar to natural sleep.(once you touch his shoulder he wakes up! In fiberoptic intubation or if I want to ask the patient something or in outpatient surgery…)
- Minimal respiratory depression, (medazolam intermittent or infusion and diazepam can cause respiratory depression)
- Airway reflexes remain intact
- Weak amnestic; no anticonvulsant properties.
- Its disadvantage : Decreases HR and BP although transient hypertension at the beginning may occur after an IV bolus.
- **Adverse effects.** Antimuscarinic effects (e.g., dry mouth and blurred vision)
- ADVANTAGE: it decreases the doses of other anesthetics when used in GA . It reduces the inhalation anesthetics and narcotic requirement we don't give too much fentanyl when using precedex
- Precedex is also used in recovery and in ICU .

# Inhalational Anaesthetics

**History of Anaesthesia** (the doctor said the history is just for your knowledge)

- Joseph Priestly – discovers $N_2O$ (nitric oxide) in 1773
- William Morton, dentist – first demonstration of successful surgical anesthesia with ether 1846 (long time ago)
- Dr. John Snow administers chloroform to Queen Victoria (1853)– popularizes anesthesia for childbirth in UK. He becomes the first anesthesia specialist.

All these drugs are not used anymore, except nitric oxide is used till now.
Because:

1) They are explosive and inflammable, so if we used ether there will be fire in the OR.
2) Also it may causes delayed induction and prolonged recovery "very bad anaesthesia".

That's why they started to think about new methods to cause rapid induction and rapid recovery, first there were new drugs like Oxyflurane and Enflurane but they caused some problems in renal failure patients, now they are not used any more. Now we only use 5 inhalational anaesthetics: N**itric oxide, Halothane, Isoflurane, Sevoflurane, and Desflurane.**

**Characteristics of the ideal inhaled anaesthetic agent:**

- Ample potency,
- Low solubility in blood and tissues,=> rapid induction & rapid recovery
- Resistance to physical and metabolic degradation,
- lack of injury to vital tissues.
- The lack of a propensity to cause seizures, respiratory irritation, and circulatory stimulation; (it shouldn't affect the CNS, cause convulsions, respiratory irritation => may cause bronchospasm or laryngeal spasm, circulatory stimulation such as hypertension or tachycardia)
- A low cost.
- Allowing the use of a high concentration of oxygen.
- The minimum alveolar concentration (MAC)"you will hear this terminology in the OR" is the volume percentage which allow 50% of the patients to stop responding to painful stimulation. So the MAC is different in every inhalation anaesthetic:
    - Halothane: 0.75%
    - Isoflurane: 1.15% - 1.2%
    - Sevoflurane: 1.85%
    - Sesflurane: 6.0% at one atmosphere

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

When you enter the OR you will see the anaesthesia machine: the monitor is showing the BP, pulse, oxygen saturation, entitled carbon dioxide and recently they started to use bispectral index (BIS) to assess the degree of the patient's sleepness (deep anaesthesia or light anaesthesia). There is also 2 vaporisers in each anaesthesia machine, the vaporisers may be Isoflurane and Sevoflurane or they may be Isoflurane and desflurane. when I start to use them I can't open them both , I can only open one. Next to that there will be the flow meter, oxygen, air and a blue button for nitric oxide which usually have a blue tube to not mix it up with the oxygen tube and cause hypoxia.
In OR we don't use 100% oxygen, usually we use 40% - 50% oxygen and the remaining is air or nitric oxide "depending on the case" and some hospitals they stopped using nitric oxide which is not a problem, but the important thing that nitric oxide usually is not given alone. So the oxygen will pass by the inhaled anaesthetics => vaporisation => into the lungs => induction of the anaesthesia

**General Pharmacokinetics:**

- The vapor pressure gives an indication of the ease with which a volatile anesthetic evaporates. **The higher the vapor pressure, the more volatile the anesthetic.**
- Blood solubility determines the speed of build-up / elimination from blood / brain
- Blood:Gas coefficient provides a measure of blood solubility
- The larger the number, the more soluble the gas in blood
- Lower blood solubility means faster induction/recovery

**Inspired air → Alveolar air → Blood → Brain**

For inhaled anesthetics, think of the blood as a pharmacologically inactive reservoir. Drugs with low versus high solubility in blood differ in their speed of induction of anesthesia. For example, when an anesthetic gas with low blood solubility, such as *nitrous oxide*, diffuses from the alveoli into the circulation, little of the anesthetic dissolves in the blood. Therefore, the equilibrium between the inhaled anesthetic and arterial blood occurs rapidly, and relatively few additional molecules of anesthetic are required to raise arterial anesthetic partial pressure, thereby rapidly achieving a steady state. Agents with low solubility in blood, thus, quickly saturate the blood. In contrast, an anesthetic gas with high blood solubility, such as *halothane*, dissolves more completely in the blood, and greater amounts of the anesthetic and longer periods of time are required to raise blood partial pressure. This results in increased times of induction and recovery and slower changes in the depth of anesthesia in response to alterations in the concentration of the inhaled drug. The solubility in blood is ranked in the following order: *halothane* > *isoflurane* > *sevoflurane* > *nitrous oxide* > *desflurane*.

Reference: Lippincott's Illustrated Review: Pharmacology (Chapter 11:IV)

## Nitrous Oxide

| | |
|---|---|
| **MAC** | 104% at one atmosphere |
| **CNS** | Mechanism: antagonism of NMDA (N-methyl-D-aspartate) receptors in CNS.<br>- Weak anesthetic, powerful analgesic<br>- Usually combined with other anesthetics.<br>- Used alone e.g. dental procedures); |
| **Cardiovascular system** | - Mild myocardial depressant and a mild sympathetic nervous system stimulant.<br>- HR and BP are usually unchanged.<br>- Increase pulmonary vascular resistance in adults. |
| **Respiratory system** | Little effect on respiration |
| **More SE** | - Nausea/vomiting<br>- Risk of bone marrow depression with prolonged use<br>- Inhibits vitamin B-12 metabolism |
| **Second Gas Effect** | Increased uptake of volatile agent when given together with N2O |
| **Expansion of closed gas spaces** | Nitrous oxide is 35 times more soluble in blood than nitrogen, Contraindicated in (e.g. air embolus, pneumothorax (if used in patients with pneumothorax or air embolus, the patient's condition will worsen; because the nitric oxide will profuse in the air embolus or in the pleural space "in a case of pneumothorax" which will make it much worse), Middle Ear Surgery (that's why in middle ear surgery/tympanoplasty they discontinue the nitric oxide before putting the graft, because if they use the nitric oxide it will cause expansion of the middle ear air and the graft may be displaced) etc) Nitrous oxide will diffuse into the cuff of ETT. So it is very important to know that nitric oxide can expand in air containing spaces and also can infuse inside the cuff of endrotracheal tube (ETT) |
| **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. so we have to be sure that there is enough oxygen to avoid diffusion hypoxia. |

## Volatile anaesthetics (Halothane, Isoflurane, Sevoflurane, and Desflurane)

| | |
|---|---|
| **Mechanism:** | Various ion channels in the CNS involved in synaptic transmission (including GABA<br>aminobutyric **acid receptors"**, glycine, and glutamate receptors) have been shown to be sensitive to inhalation anesthetics and may play a role. |
| **Metabolism** | Undergo different degrees of **hepatic metabolism**. |
| **Exhalation** | Through the lung**.** This is the predominant route of elimination |
| **CNS** | – Unconsciousness and amnesia .<br>– Dose-dependent depression of EEG (electroencephalogram) activity .<br>– Increase cerebral blood flow (CBF). |
| **Cardiovascular system** | - Produce dose-dependent **myocardial depression** and systemic vasodilation.<br>- HR tends to be unchanged, except **desflurane** (v.imp) when we use desflurane (high MAC 6%) it can cause tachycardia when we start<br>- Sensitize the myocardium to the arrhythmogenic effects of catecholamines. For exampe: in septum surgery/septoplasty they use local infiltration of adrenaline- containing lidocaine solution in nasal septum to reduce the bleeding and cause vasoconstriction. The adrenaline alone may cause arrhythmia, ventricular tachycardia and ventricular fibrillation, but when using inhalation anaesthetics (especially halothane) the possibility of these side effects increase. |

| | |
|---|---|
| **Neuromuscular system** | – Dose-dependent decrease in skeletal muscle tone => potentiate the muscle relaxant<br>– May precipitate **malignant hyperthermia (v. imp).** Malignant hyperthermia (MH) is triggered when giving the patient **succinylcholine** (used to induce muscle relaxation and short-term paralysis) or **inhalational anaesthetics**. So when the patient is asleep, the temperature will increase and CO2 will increase, after that patient may have metabolic acidosis, cardiac failure and cardiac arrest. Malignant hyperthermia is **very rare** and usually happen in patients with muscle diseases or patients who are susceptible to MH. To know if the patient is susceptible to MH, a muscle biopsy is needed "only done in few medical centres" or from family history ( if the patient have a relative passed away because of an severe hyperthermia). During the surgery if we find that the temperature and CO2 are increasing, immediately we stop the inhalational anaesthetics and remove the anaesthesia machine because there will be inhalational anaesthetics residual in the tubes, then we will try to decrease the temperature (ex.: iced water through a nasogastric tube, cold compresses and dantrolene sodium). Always remember **MALIGNANT HYPERTHERMIA with INHALATIONAL ANAESTHETICS**. |
| **Hepatic system.** | Decrease hepatic perfusion. **Rarely, ("halothane hepatitis").** |
| **Renal system** | Decrease renal blood flow . |
| **Respiratory system** | – Dose-dependent respiratory depression<br>– Airway irritation and, during light levels of anesthesia, may precipitate coughing, laryngospasm, or bronchospasm, (sevoflurane makes it more suitable ) Sevoflurane is the least one of the inhalational anaesthetics to cause airway irritation, that's why **SEVOFLURANE** is suitable in **CHILDREN induction** anaesthesia because less airway irritation (v. imp, the doctor repeated this point 3 times). You **shouldn't** do induction with isoflurane or desflurane in children, because they will cause airway irritation. So if I want to use desflurane or isofulrane in a child, I should do the induction with sevolflurane and then after that I can switch to desflurane or isoflurane.<br>– **Bronchodilator** effects, (with the exception of desflurane, which has mild bronchoconstricting activity). that's why in asthmatic patients in the OR they may have mild bronchoconstriction then relieved by the inhalational anaesthetic ( - desflurane) because of their bronchodilator effects.<br>– Inhibit hypoxic pulmonary vasoconstriction, which may contribute to pulmonary shunting. |

| | Advantages | Disadvantages |
|---|---|---|
| **Desflurane**<br>  | - Rapid onset and recovery of anesthesia<br>- (outpatient procedures)<br>- One of least metabolized to toxic byproducts | - Requires a special vaporizer<br>- **Pungent and irritating** to the airway (leading to more coughing, laryngospasm, so it is not as useful for extended surgical procedures) because it can cause irritation, not used in the induction.<br>- High inspired gas concentrations lead to a significant increase in the patient's BP & HR. if used in hugh concentration it may cause tachycardia and hypertension. |
| **Sevoflurane** (the most used inhalational anaesthetic )<br>  | - Low solubility in blood-- produces **rapid** induction and emergence<br>- **Pleasant smelling (suitable for children) (v. imp)**<br>- Has good **bronchodilating** properties and is the agent of choice in patients with asthma, bronchitis, and COPD.<br>- It has little effect on the heart rate.<br>- Minimal systemic effects-- mild respiratory and cardiac suppression | Carbon dioxide absorbents (soda lime) in anesthesia machines degrade sevoflurane to **Compound A.** This compound has been observed to cause necrosis of the proximal tubule in rats. Some studies are suggesting that the metabolism of sevoflurane through the soda lime* produce Compound A which can affect the kidneys, but this is not clinically significant. |
| **Isoflurane**<br>  | It causes peripheral vasodilation and increased coronary blood flow . | - Moderate solubility, so recovery from anesthesia may be delayed ( the fastest recovery is with the desflurane > sevoflurane > Isoflurane)<br>- Isoflurane can make the heart "more sensitive" to circulating catecholamines (like epinephrine). |
| **Halothane** (only used in poor countries because it is less expensive, we don't have the vaporiser for it in KKUH)<br>  | Used for induction in children (sweet pleasant odor); but sevofulrane is better. | Used for induction in children (sweet pleasant odor); but sevofulrane is better. |

* Soda lime: is a mixture of chemicals, used in granular form in closed breathing environments, such as general anaesthesia, submarines and recompression chambers, to remove carbon dioxide from breathing gases to prevent $CO_2$ retention and poisoning. Usually is attached to the anaesthesia machine. **- Wikipedia**

# Neuromuscular Blocking Drugs

- Used to perform 1)tracheal intubation: why do we need muscle relaxants in anaesthesia? to make the intubation easier, especially in adults, for example a 80-120 kg patient when you use the laryngoscope even when giving propofol the intubation will still be hard because there is muscle tone. In children it is possible to intubate without muscle relaxants, but the patient should be in deep anaesthesia. No doubt using muscle relaxants will make the intubation easier, the muscle tone is less, the vocal cords will be open, you can insert the tube without injuring the vocal cords.
- 2) facilitate ventilation: because the patient is on mechanical ventilation in the anaesthesia machine, so when the patient is relaxed the machine will be able to give the tidal volume, to be synchronised with the anaesthesia machine.
- 3) provide optimal surgical operating conditions, for example during laparotomy: especially in abdominal surgery, whatever is the muscle relaxant you give the surgeon will complain that the muscle tone is high and there is a risk of the bowel going out. So we have to use an efficient muscle relaxant to relax the abdominal muscles.

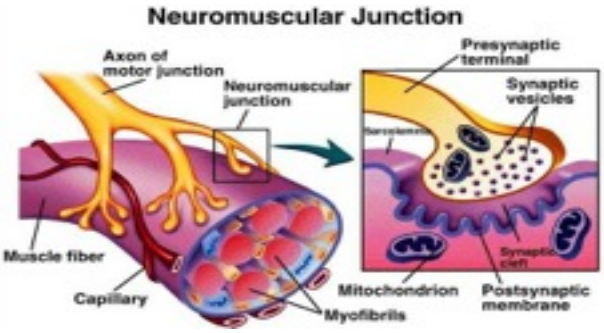



**Table 9–1.** Depolarizing and nondepolarizing muscle relaxants.

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

We have two groups of muscle relaxants:

1) Depolarizing (only one): Succinylcholine (suxamethonium)
2) Nondepolarizing: Short/intermediate/long acting

lately we started to use the intermediate acting instead of the long acting, because it was found that when using long acting muscle relaxants and the patient is very relaxed for long duration => patient may have post operative pulmonary complications. So most commonly we are using the intermediate acting and we usually use the nerve stimulator to know if the effect of the drug is finished or not, so can give supplement doses. We used to give long acting to make sure that the patient is relaxed and he will not move during the surgery when the muscle relaxant effect is finished, but now because of the nerve stimulator we can monitor the muscle relaxant which make is easier and safer to use the intermediate acting muscle relaxants. Intermediate acting also have another advantage, let's say the surgery was planned to take 2 hours but the surgeon finished in half an hour, in this case we can wake the patient up.

A. **Depolarizing(Succinycholine)**

- Structurally similar to acetylcholine and function as competitive inhibitors.
- Very short duration of action: it act within 60 seconds, duration about 5 minutes.
- **Metabolized very quickly by an enzyme called plasma cholinesterase. (v. imp)**
- A useful drug in situations where muscle relaxation is needed for only a short time such as to facilitate intubation.

Now Succinycholine is not used that much, we use it mainly in rapid sequence induction (RSI): if we have a pregnant patient will have emergency CS and she didn't fast and with her pregnancy "delayed gastric emptying", so even of she is fasting for 8 hours there will be some gastric content in the stomach, in this case there is a risk of vomiting and aspiration. So we need to put the tube immediately and we need a muscle relaxant once given it will start a rapid onset of action, and the only muscle relaxant to give this effect is Succinycholine.
SUCCINYLCHOLINE IS V. IMP IN RAPID SEQUENCE INDUCTION IN FULL STOMACH PATIENTS & ER patients (in RTA patients you don't know if the patient is fasting or not).

- **Side effects of Succinycholine:**

- **Myalgia:** is common postoperatively, especially in the muscles of the abdomen, back, and neck. Because the Succinycholine cause muscle fasciculations (muscle movement then relaxation) which will lead to muscle pain in abdomen, back and neck.
- **Cardiac dysrhythmias: sinus bradycardia (especially in repeated dose, for example I gave the patient succinylcholine and I couldn't intubate him and the effect of the succinylcholine is gone, so I have to give another dose and try again. So it is used in RIS and difficult intubation)**, junctional rhythm, and even asystole after the first dose in children and following repeated exposure within a short time interval (i.e., 5 minutes) in adults.
- **hyperkalemia:** especially in major burns, massive tissue injuries, extensive denervation of skeletal muscle, or upper motor neuron diseases. Succinylcholine when given it increases the potassium from 0.5-1 mEq/l, this is not a problem in healthy adult patients but it may cause a serious problem in burn patients because they already have hyperkalemia and with succinylcholine the potassium may reach to 7 and the patient will have cardiac arrest.
- **A transient increase in intraocular pressure.**
- **Increased intragastric pressure: because it increases the intraabdominal pressure because of the fasciculations**
- **Increase in intracranial pressure: so in head trauma it is better to avoid succinylcholine**
- **Malignant hyperthermia (MH):** a dramatic increase in body temperature, acidosis, electrolyte imbalance and shock. As we said before succinylcholine and inhalational anaesthetics can trigger MH.

- **Succinycholine apnea (Prolonged blockade):** following SCh may be caused by low levels of plasma cholinesterase as in severe liver or kidney disease, a drug-induced inhibition of its activity, or a genetically atypical enzyme => the affect of succinylcholine will be prolonged. So I gave the patient SCh and propofl and I expect the drug effect will finish after 5 minutes, how I will know that the effect is finished? the patient will start swallowing, breathing, movement, or with the nerve stimulator i will find the patient's fingers are moving, in case i didn't see any of these signs that means the patient has Succinycholine apnea. how to treat? ventilate the patient until reversed or 10 ml blood transfusion to increase the levels of plasma cholinesterase.
- **Anaphylaxis:**. Suxamethonium is responsible for over 50% of anaphylactic reactions to NMBDs.

- **Side effects :**
  - Fasciculations .
  - Muscle pain
  - Bradycardia.
  - Increases in ocular and gastric pressure,
  - Hyperkalemia .
  - Anaphylaxis.
  - Malignant hyperthermia: a dramatic increase in body temperature, acidosis, electrolyte imbalance and shock

B. **<u>Nondepolarizing blockers</u>**

- They act by competitively blocking the binding of ACh to its receptors and inhibit muscular contraction.
  - **It is characterized by :**
    - Absence of fasciculations. once you give it the patient will be gradually relaxed. Enters to neuromuscular block, first it starts to close laryngeal muscle and diaphragm, and finally the abdominal muscles and the limbs
    - Potentiation by other nondepolarizing NMBDs and volatile anesthetic agents. that means if I gave 2 muscle relaxants, both drugs will potentiate each other = increase in the muscle relaxant effect of each drug. And if given with volatile (inhalational) anaesthetic agents ,which also decrease the muscle tone, both the nondepolarizing blockers and inhalational anaesthetics will increase the muscle relaxation.
    - Reversal by AChE inhibitors. when giving neuromuscular block, in the end of the surgery I want the patient to start to take a breath and to move, I can't just remove the tube, because after removal of the tube the patient may not be breathing, or he is breathing but weak breathing (tidal volume low), or maybe he is breathing but after some time he will stop because of some residual muscle relaxant in the neuromuscular receptors, for all these reasons we should use a reversal (such as Neostigmine)

## I. Mivacurium

- Short-acting non-depolarizing NMBD .
- It is rapidly hydrolyzed by plasma cholinesterase.
- Used with caution in patients with known atypical plasma cholinesterase activity or using cholinesterase inhibitors. because there may be prolonged duration of action.
- Histamine release causing a transient decrease hypotension and tachycardia (disadvantage). Whenever a muscle relaxants is causing a histamine release, this is considered as a disadvantage. Because the histamine release may cause bronchospasm in bronchial asthma patient. So you should avoid histamine releasing muscle relaxants in asthmatic patients.
- If reversal required , with an anticholinesterase agent, edrophonium may be preferred to neostigmine because it has much less effect on plasma cholinesterase activity. Which means if you want to reverse the Mivacurim in patients with atypical plasma cholinesterase activity, or low levels of plasma cholinesterase, the best reversal (anticholinestrease) to use in the case is Edrophonium better than the Neostigmine.

## II. Atracurium besylate (Tracrium)

- Widely used and have an intermediate onset and duration of action (20-30 mins). Here in KKUH, Atracurium was widely used for a long time, but now there is a new drug which is better => Cisatracurium.
- It causes **release of histamine** (disadvantage) but has no direct cardiovascular effects (advantage). **MCQs:** what's the muscle relaxant that can cause histamine release? ATRACURIUM
- *Metabolism* is by **Hofmann degradation and ester hydrolysis** in the plasma, hence its duration of action is independent of renal and hepatic function **(v. imp) (advantage). MCQs:** Which drug is suitable for patients with renal or hepatic dysfunction? ATRACURIUM, (why?) because it is independent of renal and hepatic function.
- A breakdown product of atracurium, laudanosine may accumulate due to very slow hepatic metabolism and upon crossing into the brain may cause seizures. This is not clinically significant, what you should know about atracurium: Histamine release & Suitable for patients with hepatic or renal dysfunction because it is metabolised by Hofmann degradation and ester hydrolysis in the plasma.

## III. Cisatracurium(Nimbex)

- Isomer of atracurium
- Less laudanosine formed (advantage, the reason why Cisatracurium is preferred over atracurium).
- **Unlike atracurium it does not release histamine**. **MCQs:** Patient with bronchial asthma, which muscle relaxant is suitable? CISATRACURIUM.
- It is *metabolised* by Hofmann degradation and does not accumulate in renal failure. So if you have a patient with renal failure and you can choose between Atracurium and Cisatracurium, you should choose Cisatracurium because it doesn't release histamine.

IV. **Vecuronium bromide(Norcuron)**

- Vecuronium is structurally similar to pancuronium but has a slightly faster onset and shorter (intermediate) duration of action.
- Advantage: It does not release histamine or **have any cardiovascular effects (v. imp)** that's why anaesthetist always use it with cardiovascular patients, because it has no cardiovascular effect.
- *Metabolism* in the liver (disadvantage) occurs active metabolites before being excreted in the bile and urine. Not used in hepatic patients.
- Vecuronium has a prolonged clinical effect in elderly patients and those with liver disease.

V. **Rocuronium**. (Zemuron)

- An analog of vecuronium. Recuronium is used as an alternative for Succinylcholine because of it is rapid onset.
- **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. When you increase the dose, you will prolong the duration of action.
- Used when a rapid sequence induction is required if SCh is contraindicated.
- An intermediate duration of action .
- *Metabolised* in the liver and excreted in the bile.
- In renal failure ------in a longer duration of action
- Minimal cardiovascular effects .
- Does not release histamine,
- Higher incidence of anaphylactic reactions
- There is a new drug called Sugammadex, very expensive (about 1000 SR), is usually used as an alternative for Succinylcholine. Induction by rocurnoium in difficult intubation cases,let's say I couldn't insert the tube and now i want to wake up the patient, the recronium will last for half an hour, what should i do? Give sugammadex, it will go into the plasma and incapsulate the recuronium (sugammadex eats recuronium), the effect of the recronium will go rapidly and the patient will wake up. The problem with sugammadex that it is really expensive compared to Succinlycholine (only 5 SR), because of the high cost of the sugammadex, it is only used in limited cases in KKUH like in CS as a substitute for Succinylcholine, so we give Recuronium and Sugammadex (the sugammadex is only for your knowledge).

Many anaesthetists use rocuronium in place of suxamethonium for rapid sequence induction (RSI). This is less common in obstetric anaesthesia as the duration of action of an effective dose of rocuronium exceeds most obstetric procedures. Sugammadex offers the possibility of rapidly reversing profound rocuronium neuromuscular blockade at the end of surgery.
Refrence: http://www.ncbi.nlm.nih.gov/pubmed/21480829

VI. **Pancuronium bromide (Pavulon)**

- The first steroid NMBD in clinical use has a slow onset and **long duration** of action.
- It does not cause histamine release
- Weak sympathomimetic properties and causes tachycardia.
- It is partly de-acylated in the liver to a metabolite with neuromuscular blocking properties, and partly excreted unchanged in the urine.
- Its action is prolonged in renal and hepatic impairment.

**The most suitable drug for renal and hepatic patients is Cisatracurium and atracurium.**

- **Clinical Choice of NMBD: How to choose the proper NMBD?**
  - **Urgency** for tracheal intubation, such in CS, i have to intubate very fast => use SCh
  - **Duration** of the procedure, if the procedure will take 15 minutes, i will think of Mivacurium (short duration of action), if the procedure will take 8 hours, i may use Vecuronium.
  - **Coexisting medical conditions** that may affect the NMJ, and side effects and metabolism. As i said before in hepatic and renal patients use Cisatracurium or atracurium. in IHD patients, avoid drugs causing trachycardia. In head trauma or brain tumour patients, avoid SCh because it increases the ICP. etc
  - **Cost-effectiveness**

➢ SCh makes it a good choice for rapid intubation of the trachea,
➢ Rocuronium will decrease the risk of hyperkalemia in patients with burns. Recuronium is a substitute for SCh without the risk of hyperkalemia.
➢ Pancuronium can produce a tachycardia that is undesirable in patients with severe IHD, but its vagolytic effects may be appropriate in pediatrics.

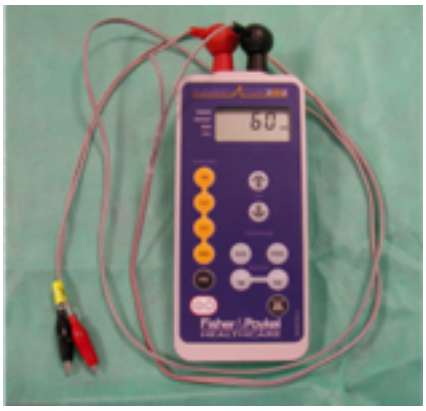
**Anticholinesterases (Neostigmine):**

- At the end of the surgery you have to reverse the effect of the neuromuscular blocker (non depolarizing) so you have to use Neostigmine. if you see the syringe of the neostigmine, it is written neostigmine+atropine or neostigmine+glycopyrrolate.
- (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 include the ability to lift the head from the bed for 5 seconds,
- No role for anticholinesterases in reversing the effects of suxamethonium.
- Before the end of the surgery I must try to decrease the doses of the muscle relaxants given, because when i give neostigmine the effect of the muscle relaxant should be 70% to 90% not 100%, if the effect was 100% the neostigmine will not work or it may take longer to reverse. clinically we know that the effect of the muscle relaxant is gone by spontaneous breathing & nerve stimulator.
- **Intravenous injection at a dose** of 0.05 mg/kg (maximum 5mg).

- **Neostigmine Side effects:**
  - Bradycardia (that's why we combine it with either atropine or glycopyrrolate) (v.imp), miosis, GI upset,
  - Nausea, bronchospasm (it can cause a problem in patients with bronchial asthma), increased bronchial secretions, sweating and salivation (atropine decreases the 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.

**Peripheral nerve stimulator**

- Check the depth of neuromuscular blockade, it tells me the degree of muscle relaxation (fully relaxed, 50%, 70%)
- Determine that neuromuscular blockade is reversible
- At least 3 twitches on a train of four (4 fingers) should be detected before attempting reversal.
- the nerve stimulator is either a separate device or incorporated in the anaesthesia machine.



# Local Anaesthetics (LAs)

- Not all patients need general anaesthesia, for example in ophthalmic surgery (cataract surgery) they are using retrobulbar block by local anaesthetics.
- LAs are drugs which reversibly prevent the transmission of pain stimuli locally at their site of administration. that means that the effect of the analgesia is in the site of administration.
- **Mechanism** : reversibly blocking sodium channels to prevent depolarization inside the nerve.
- **Lipid solubility** (the effect of onset or duration of LAs depends on their lipid solubility, with increased lipid sloubility, there will be rapid onset of action**)** : determines, potency, plasma protein binding and duration of action of local anesthetics.
- **Addition of vasoconstrictor:** Sometimes we add adrenaline(vasoconstrictor) wil LAs (why?)
    1. Prolongation of anesthetic action, because some of LAs cause vasodilatation => gradually will disappear from the site of infiltration and, for example the LA usually stay for 30 minutes, in this case it will decrease to only 20 minutes.
    2. Decreased risk of toxicity, so I don't have to give large doses of LAs, because it can cause toxicity.
    3. Decrease in bleeding from surgical manipulat, such in septoplasty, they use lidocaine with adrenaline.

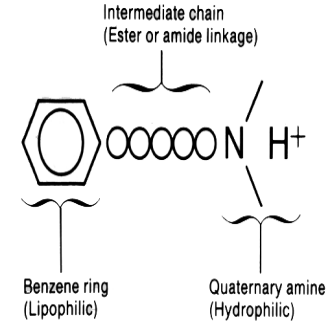
**Local anaesthetics are divided into two groups:**

**1. Esters** (metabolized by plasma cholinesterase)

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

**2. Amides** (metabolized by cytochrome p-450 (the liver)) (amides group is used more the esters group)

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



| Applications of local anesthesia: |
|---|
| • **Nerve block**: (e.g., dental and other minor surgical procedures) for example the brachial plexus supply the upper limb, so we do brachial plexus block, we insert the needle near the brachial plexus and we inject LAs => distribute around the brachial plexus => block of upper limb => you can operate on this patient's arm while he is awake for 2-3 hours. |
| • **Topical application**: to skin for analgesia (e.g., benzocaine) or mucous membranes (for diagnostic procedures). Lidocaine spray on mucus membrane, lidocaine gel on skin, EMLA cream (prilocaine and lidocaine cream) for paediatric patients prior to insertion of an IV needle. |
| • **Spinal & epidural anesthesia**: we can use lidocaine and marcaine, lidocaine for rapid onset and marcaine for prolonged duration of action to decrease the risk of toxicity. |
| • **Local infiltration**: at end of surgery to produce long-lasting post-surgical analgesia (reduces need for narcotics). for example a patient did an appendectomy, after the surgery we can do local infiltration in the ward sub-cutaneously, this will decrease the pain. also in paediatric patients with cut injury, we will start with local infiltration sub-cutaneously then we will do the stitch. |
| • **I.v. infusion**: for control of cardiac arrhythmias (e.g., lidocaine for ventricular arrhythmias) |

- **Choice of local anesthetics**
  - Onset
  - Duration
  - Sensory (lidocaine & Ropivacaine) vs. motor (Bupivicaine**)** block
  - Potential for toxicity, the most toxic drug is the Bupivicaine, so make sure not to give high doses or as an IV injections.

### -1- Lidocaine

- Amide type anesthetic
- Lidocaine was introduced in 1948
- The most commonly used local anesthetic
- Rapid onset and a duration of 60-75 minutes, duration of action can be extended if we use vasoconstrictor such as epinephrine.
- 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. in intensive care they use lidocaine for management of ventricular tachycardia

## -2- Bupivicaine

- Amide-type local anesthetic
- Introduced in 1963
- Onset of action is **slower** than lidocaine and anesthesia is **long acting** .
- Normally provides 2-4 hours of anesthesia
- Can be extended in some cases by using solution with epinephrine to 7 hours.
- More **cardiotoxic** (v. imp) than lidocaine, difficult to treat. for example while doing a brachial plexus block, you may inject it by mistake in the vein, so you should aspirate first before you inject to make sure that there is no blood and you are in the nerve.
- Metabolized in the liver and excreted by the kidneys
- Contraindicated for use in pts with known hypersensitivity

## -3- Ropivacaine

- New drug, recently introduced in KKUH OR
- A less toxic, long-lasting LA.
- Undergoes extensive hepatic metabolism after IV administration, with only 1% of the drug eliminated unchanged in the urine.
- Ropivacaine is slightly less potent than bupivicaine .
- It has become one of the most commonly used long acting LAs in peripheral nerve blockade.

In OR the most commonly used LAs: Lidocaine, bupivicaine and ropivacaine.

**Local Anesthetic Toxicity:** what you expect with LAs toxicity?!

- **Central nervous system** (excitation followed by depression)
  - initially-- lightheadedness, circumoral numbness, dizziness, tinnitus, visual change. First sign of lidocaine toxicity is numbness of the lips. Lidocaine toxicity also can happen in intensive care, for example the infusion rate is 5 ml/hr and the nurse changed it by mistake to 15 ml/hr => may lead to toxicity.
  - later-- drowsiness, disorientation, slurred speech, loss of consciousness, convulsions
  - finally-- respiratory depression , comatose
- **Cardiovascular:** Myocardial depression and vasodilation-- hypotension and circulatory collapse
- **Allergic reactions**-- rare (less than 1%) happens more with esters group
  - preservatives or metabolites of esters
  - rash, bronchospasm

### Prevention and Treatment of Toxicity

- Make sure of the route of administration &dose. In case of toxicity, first: supportive treatment: respiratory depression => ETT & mechanical ventilation. Circulatory collapse => IV fluids, vasopressors. For Bupivicaine cardiac toxicity => give intralipid.

*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)