PHARMACOLOGY OF ANAESTHETICS

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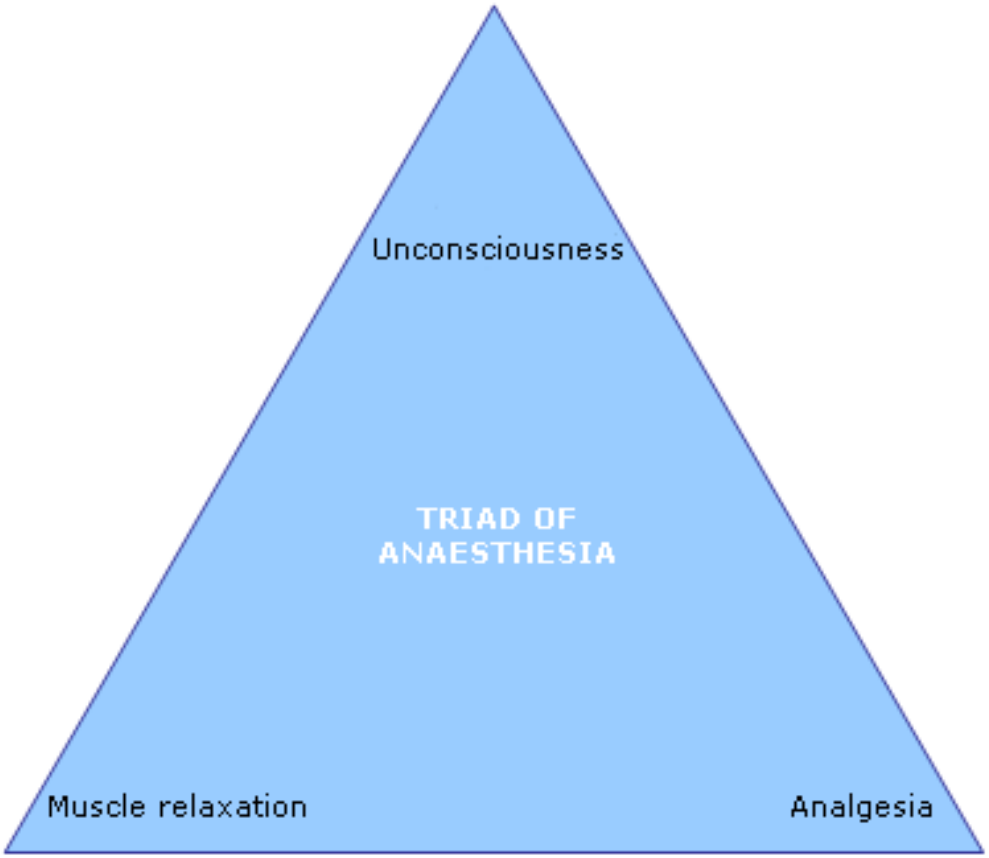
AIMS OF ANAESTHESIA



Triad of anaesthesia

- **Analgesics** IV/regional anaesthesia or analgesia
- **Anaesthetic agents** to produce unconsciousness
- **Neuromuscular blocking agents** for muscle relaxation

Why unconscious patient require analgesia ?

Overview

- Intravenous and inhalational anaesthetics
- Analgesics – simple, opioids
- Muscle relaxants
- Decurarization

INTRAVENOUS ANAESTETICS

Stages of anaesthetics

- **Induction** – putting asleep
- **Maintenance** – keeping the patient asleep
- **Reversal** – waking up the patient

Intravenous anaesthetics

- Onset of anaesthesia within one arm – brain circulation time – 30 sec
- Effect site ➡ brain
  - Propofol
  - Thiopentale
  - Etomidate
  - Ketamine
  - BZD

General anaesthetic-how do they work

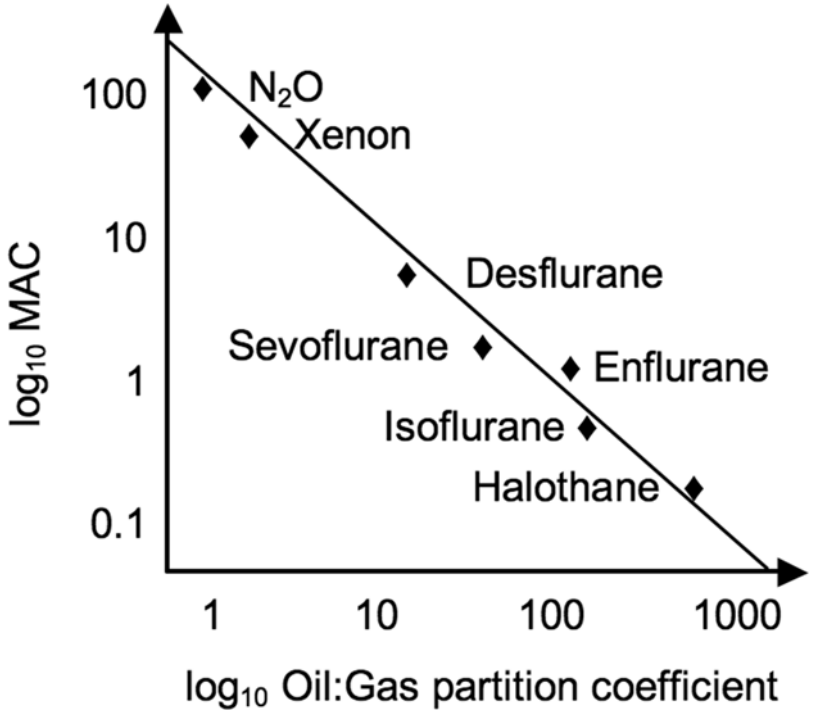
- **TASK – EXPLAIN**
  1. Loss of conscious awareness
  2. Loss of response to noxious stimuli
  3. Reversibility

- Anatomical site of action
  - Brain : thalamus, cortex
  - Spinal cord

Molecular theories

\\credit:
Cambridge University Press

Meyer-Overton hypothesis



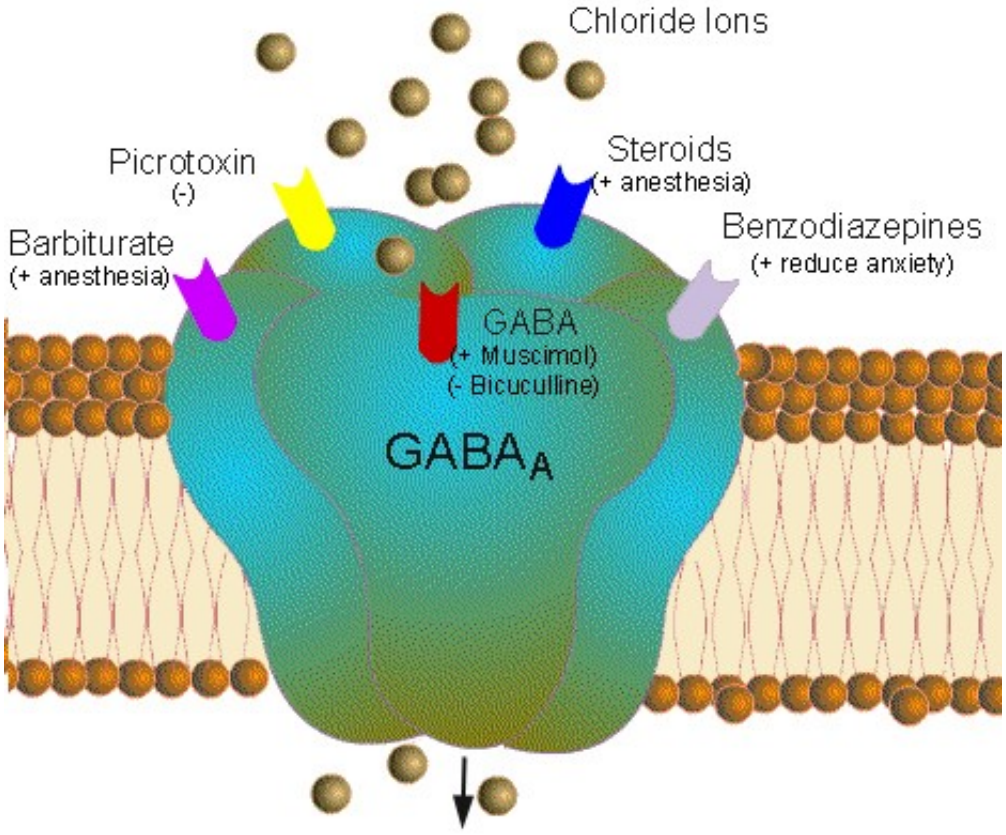
- Linear correlation between the lipid solubility and potency

Molecular theories

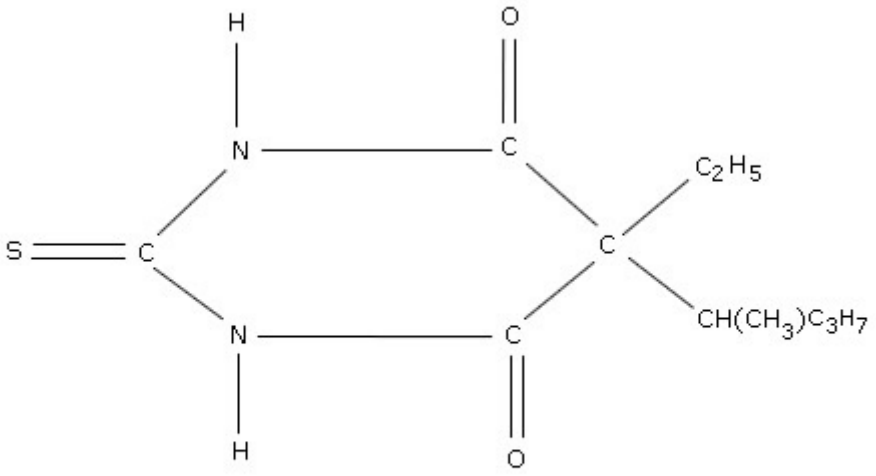
- Critical volume hypothesis
  - Disruption of the function of ionic channels
- Perturbation theory
  - Disruption of annular lipids assoc. with ionic channels
- **Receptors**
  - **Inhibitory** – $GABA_A$, glycin ⟵ enhance
  - **Excitatory** - nAch, NMDA ⟵ inhibit

$GABA_A$ receptor

- ionotropic receptor



Thiopentale

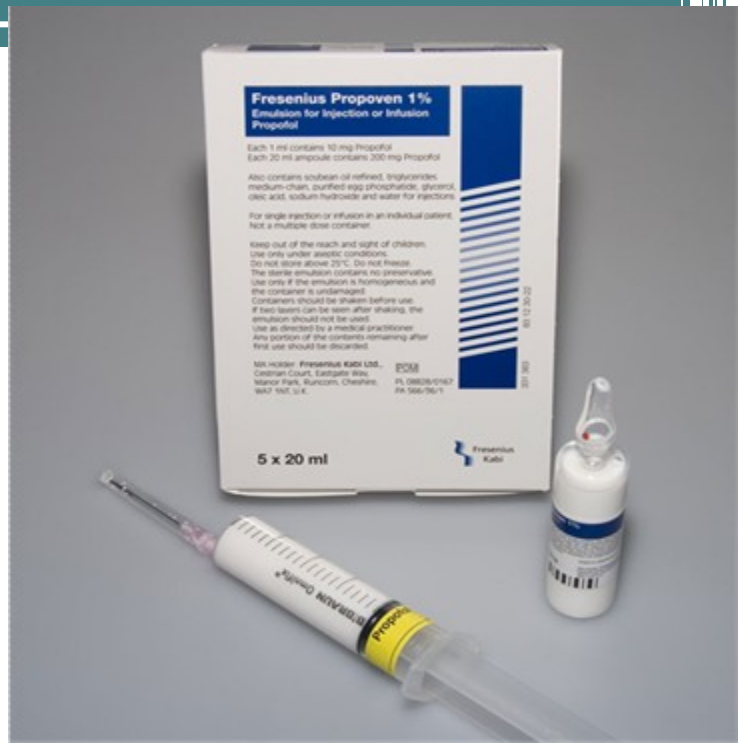


- Barbiturate
- **Dose** 3-7 mg/kg
- **Effects** : hypnosis, atiepileptic, antanalgesic
- **Side effects**
  - CVS: myocardiac depression, ↓CO
  - Reduction in MV, apnea

Thiopentale

- **Problems with use**
  - Extremely painfull and limbtreatening when given intra-arterially
  - Hypersensitivity reactions 1: 15 000
- **Contraindications**
  - Porphyria

Propofol



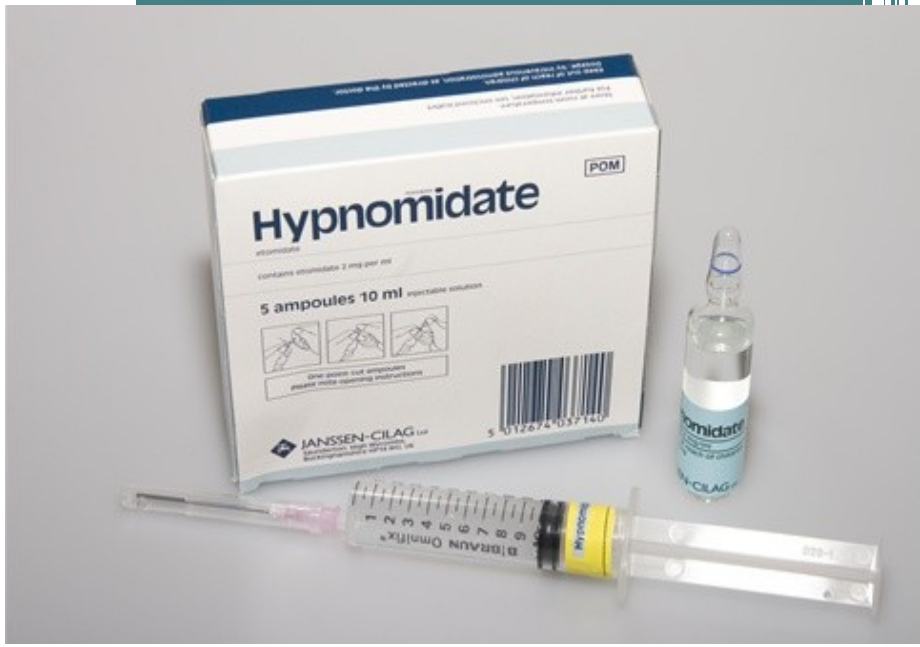
- Phenolic derivative
- **Dose** 1- 2.5 mg/kg
- **Effects** : hypnosis
- **Side effects**
  - CVS: myocardiac depression, ↓SVR, ↓CO
  - Respiratory depression
  - Hypersensitivity 1 : 100 000

Propofol

- Other effects
  - Pain on induction
  - Nausea and vomiting less likely
  - Better for LMA placement then thiopentale

- Relative **contraindications**
  - Children under 3

Etomidate



- Ester
- **Dose** 0.3 mg/kg
- **Effects** : hypnosis
- **Side effects**
  - CVS: very little effect on HR, CO, SVR
  - Minimal respiratory depression

Etomidate

- **Problems with use**
  - Pain on injection
  - Nausea and vomiting
  - Adrenocortical suppression
  - Hypersensitivity reaction 1: 75 000

- **Relative Contraindications**
  - Porphyria

Ketamine

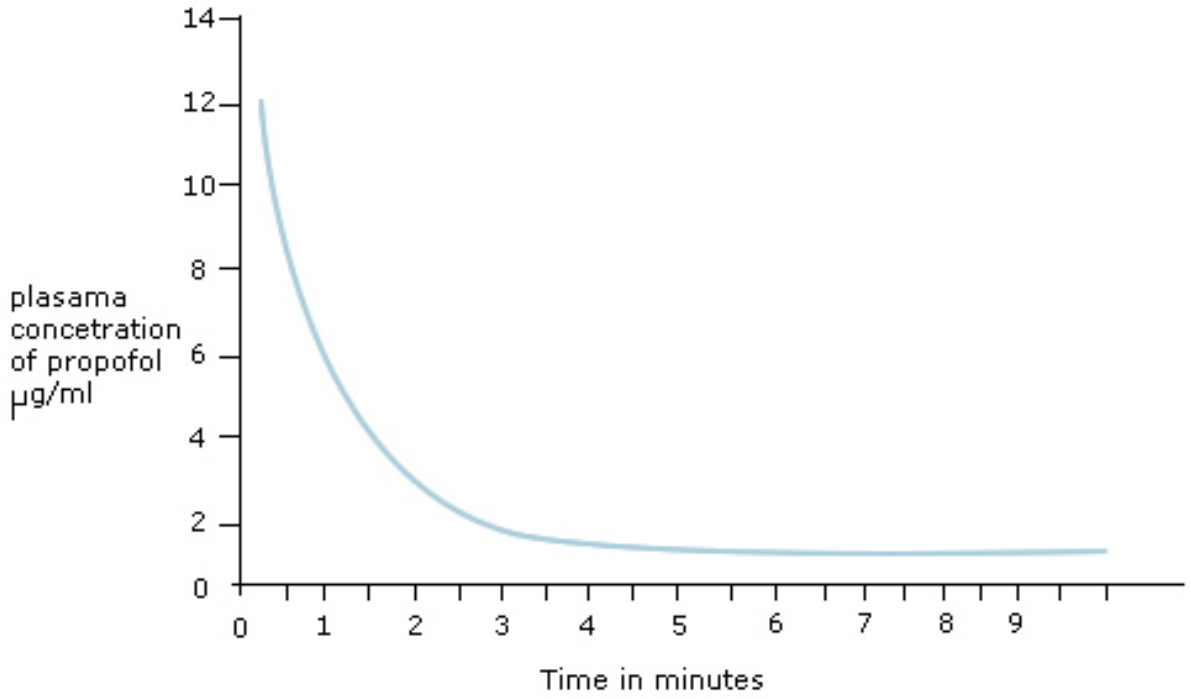
- Phencyclidine derivative

- CV effects - ↑ **HR, BP**, CO, O2 consumption
- RS - ↑ RR, preserved laryngeal reflexes
- CNS – **dissociative anaesthesia**, **analgesia**, amnesia

- Use – analgesic in Emerg. Med

Pharmakokinetics

- Recovery from propofol single bolus 5-10 min

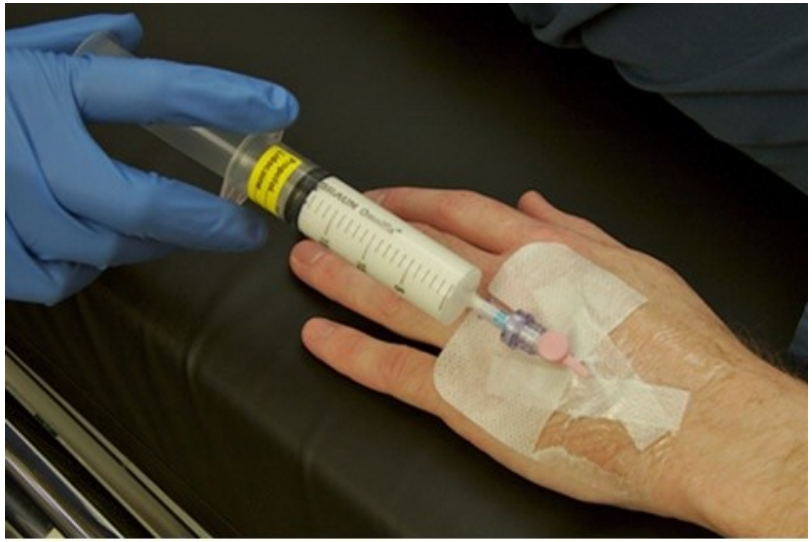


Choice of induction agent

- 1. Are any agents absolutely contraindicated ?
  - Hypersensitivity, porphyria
- 2. Are there any patient related factors ?
  - CVS status
  - Epilepsy
- 3. Are there any drug related factors ?
  - Egg allergy

Induction + maintenance

- **TIVA** (=Total Intravenous Anesthesia)



SUMMARY – IV anaesthetics

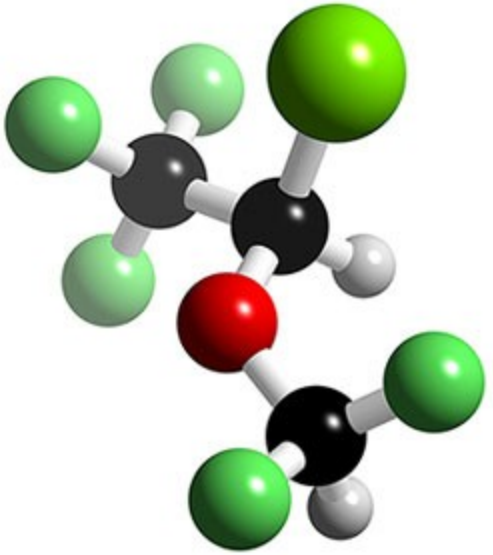
- Mechanism of action – via receptors
- Used for anaesthesia and sedation
- Used for induction
  - thiopentale, propofol, etomidate
- Propofol used for maintenance as well

- Most of them cause CV and respiratory depression

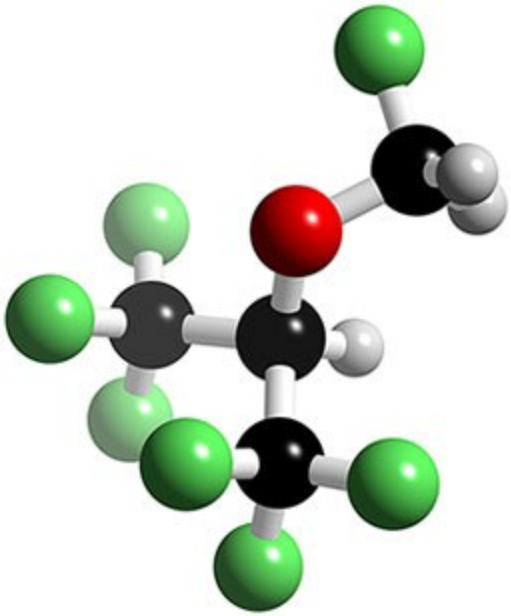
INHALATIONAL ANAESTETICS = volatile anesthetics

Anaesthetic gases

- Isoflurane
- Sevoflurane



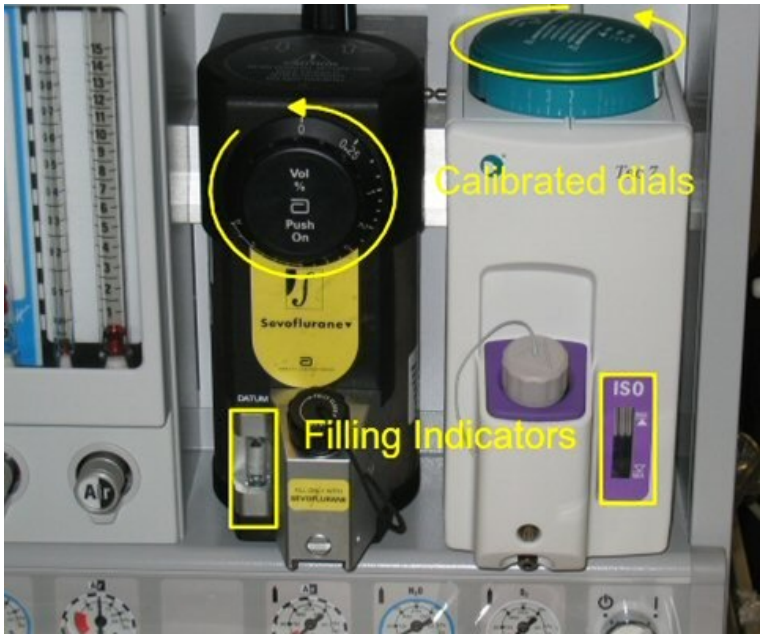
- Halothane
- Enflurane
- Desflurane



- N_2O – nitrous oxide

Anaesthetic gases

- Any agent that exists as a liquid at room temperature is a **vapour**
- Any agent that cannot be liquefied at room temperature is a **gas**
  - Anaesthetic ‘gases’ are administered via **vaporizers**



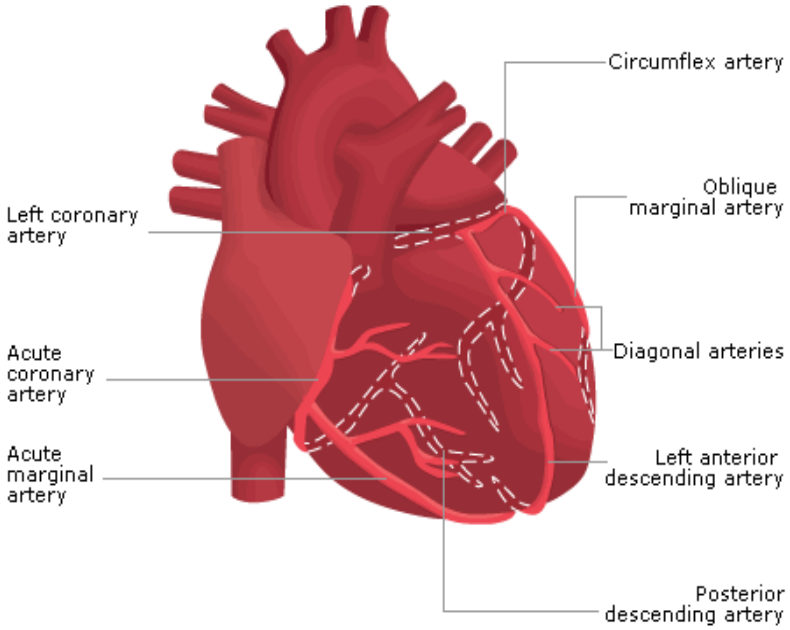
Potency

- MAC – that concentration required to prevent 50 % of patients moving when subjected to standart midline incision

- Sevoflurane MAC 1.8 %
- **Isoflurane MAC 1.17 %**

Respiratory and cardiovascular effects

- All volatile anaesthetics cause ↓ MV and ↑RR
- Isoflurane is irritant vapour
- ↓ SVR, blood pressure falls, ↑ HR
- Isoflurane - ? Coronary steel



Metabolism and toxicity

- Isoflurane (0.2 %)and Sevoflurane(3.5%) are metabolized by liver
- **F^-** ions are produced - ? Renal impairment
- Iso and Sevo trigger **malignant hyperthermia**
- N_2O
  - Megaloblastic anaemia
  - Teratogenic
  - PONV

SUMMARY – inhalational anaesthetics

- Mechanism of action – via receptors
- Used for induction (sevoflurane)
- And maintenance of anaesthesia
- Commonly used : Sevoflurane, Isoflurane
- Dose dependent CV and respiratory depression
- All, but N2O trigger malignant hyperthermia

NEUROMUSCULAR BLOCKING AGENTS = NMBAs

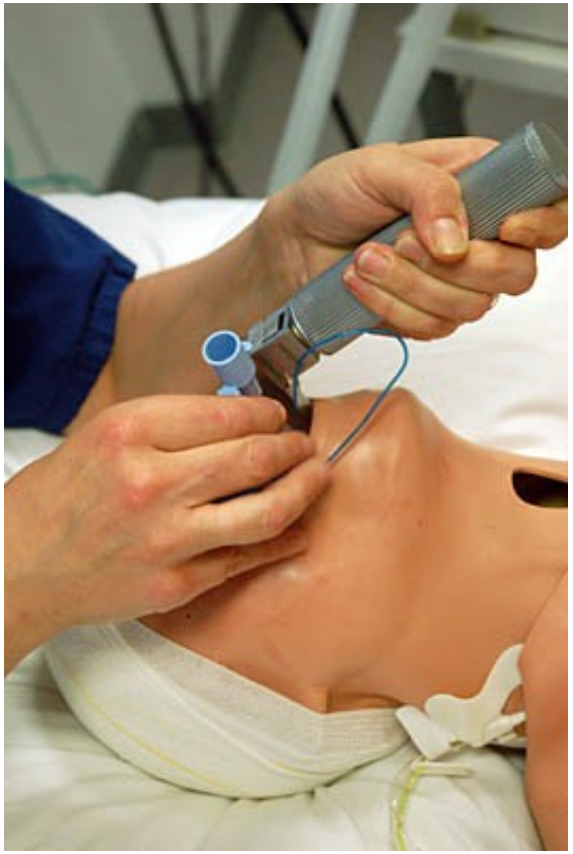
Neuromuscular blocking agents

- Exclusively used in anaesthesia and intensive care

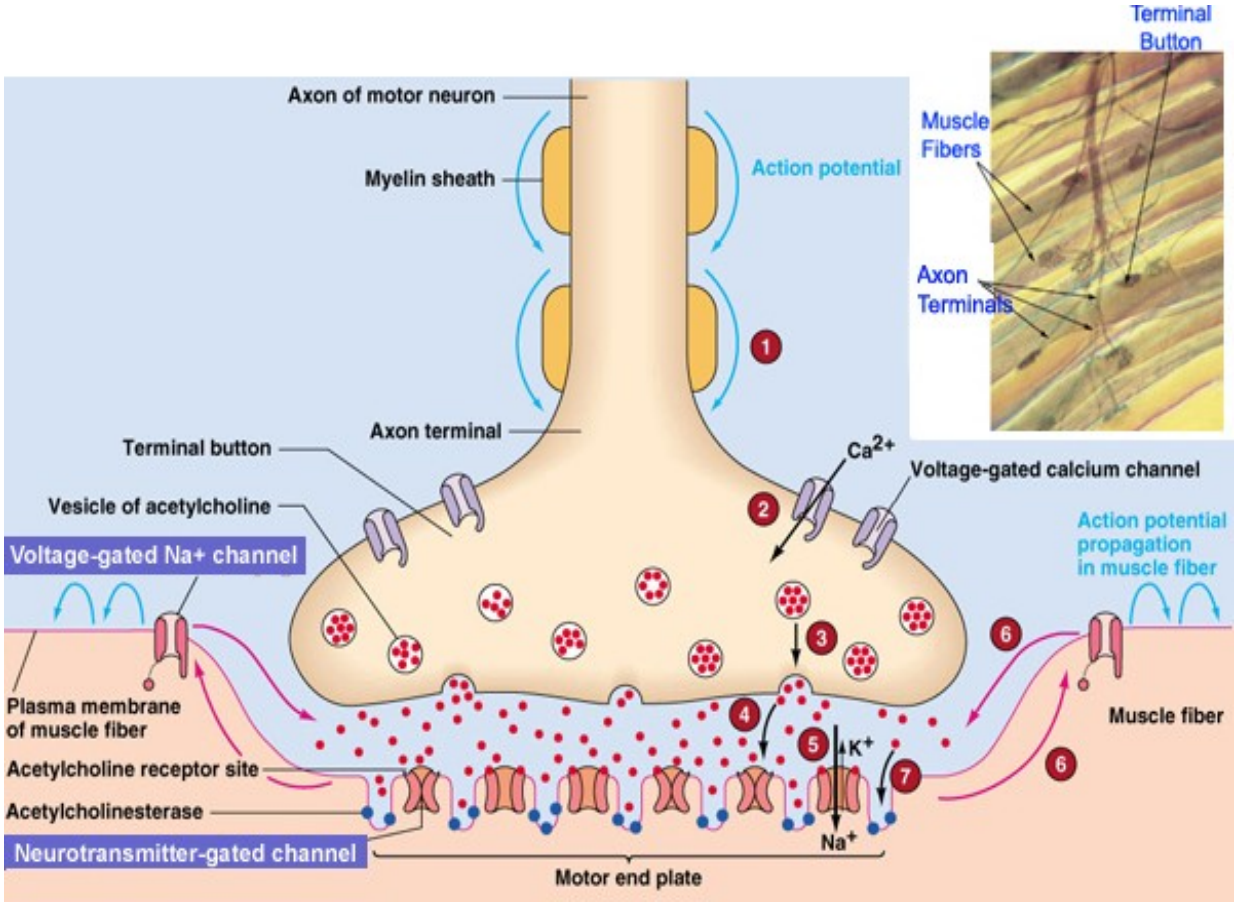
- Two classes
  - Depolarizing
    - succinylcholine
  - Non depolarizing
    - Vecuronium, rocuronium - aminosteroid
    - Atracurium, cisatracurium - benzylisoquinolinium

Use of NMBAs

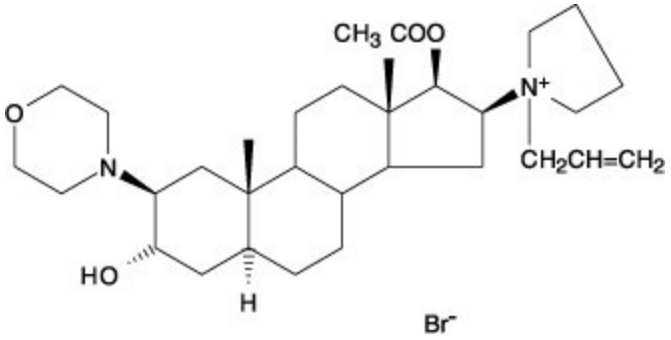
- Tracheal intubation
- Surgery where muscle relaxation is essential
- Mechanical ventilation



Neuromuscular junction



Mechanism of action



- Depolarizing
  - structurally related to Ach (=acetylcholine)
  - first activating muscle fibres, then preventing further response
  - short acting drugs

- Non depolarizing
  - compete with Ach at nicotinic receptor at the neuromuscular junction
  - middle and long acting drugs

Choice for tracheal intubation

Elective surgery	Emergency surgery
Standart induction	Rapid sequence induction
Non depolarizing agent	Succinylcholine or rocuronium

Intubating doses

Succinylcholine	1 – 2 mg/kg AcBW
Rocuronium	0.6 - 1 mg/kg IBW
Atracurium	0.5 mg/kg IBW

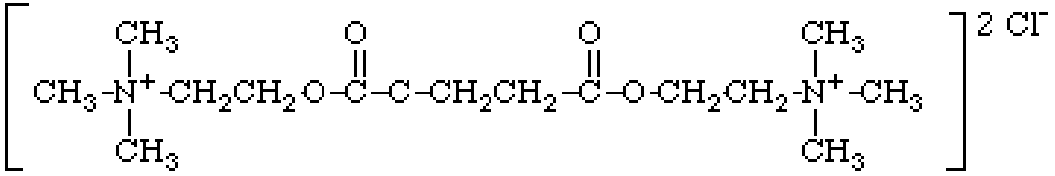
To maintain paralysis

- Non depolarizing muscle relaxants

Succinylcholine	No
Rocuronium	maintenance dose: 0.1 – 0.2 mg/kg
Atracurium	maintenance dose: 0.1 – 0.2 mg/kg

Succinylcholine pharmacokinetics

- Duration of action : 3 – 6 min (full recovery over 10 min)
- Metabolism – plasma cholinesterase
  - Cave: suxamethonium apnea



Succinylcholine - adverse effects

- Bradycardia
- Muscle pain – ‘sux’ pain
- Transient raised pressure in eye, stomach and cranium
- Raise in potassium !!

Succinylcholine - contraindications

- Patient related contraindications
  - Malignant hyperpyrexia
  - Anaphylaxis to SCh
  - Succinycholine apnea / Pseudocholinesterase deficiency
- Clinical contraindications
  - Denervation injury / long term immobilized patient
  - Patient with burns
  - Penetrating eye injury

Non depolarizing muscle relaxants

- Choice of NMBs
  - Personal preference
  - Atracurium or cisatracurium better in renal or hepatic failure
  - Avoid atracurium in asthmatic patients – cisatracurium is drug of choice
  - Rocuronium (or vecuronium) could be reversed (by antidotum sugammadex)

Comparison of Pharmacokinetics between nondepolarising neuromuscular blocking agents[1]

Neuromuscular Blocking Agents	Dosing	Onset time	Duration	Pharmacokinetics, Precautions and Side Effects
Rocuronium	0.6mg/kg (2 x ED_{95}) maintenance dose: 0.1mg/kg or infusion at a dose of 5-12mcg/kg/minute	1.5-3 minutes	30-70 minutes	Fastest onset time, alternative to succinylcholine for rapid sequence intubation Volume of distribution of 0.3-0.7L/kg, excreted mainly through biliary route
Vecuronium	0.1mg/kg or 2 x ED_{95} for 3-4 minutes maintenance dose: 0.01mg/kg or an infusion at 1-2mcg/kg/min	3-4 minutes	25-50 minutes	Volume of distribution of 0.4 L/kg, Neuromuscular monitoring is required for patients with renal or hepatic disease that may have prolonged response to vecuroniu
Pancuronium	0.1mg/kg (1.5 x ED_{95}) for 3-5 minutes maintenance dose: 0.02mg/kg	3-5 minutes	60-120 minutes	Rarely used due to high incidence of postoperative residual neuromuscular weakness and cause tachycardia due to direct sympathomimetic stimulation and blockage of cardiac muscarinic receptors. Volume of distribution of 0.2 to 0.3 L/kg, eliminated mostly through the renal route, with 20 percent biliary excretion, avoided in patients with renal and hepatic impairment
Atracurium	0.5 mg/kg, or 2 x ED95 for 3-5 minutes maintenance dose: 0.1mg/kg or an infusion rate at 10-20 mcg/kg/min	3-5 minutes	30-45 minutes	side effects: skin flushing, hypotension and tachycardia due to the increase in plasma histamine level Volume of distribution is 0.15L/kg, metabolism of Atracurium is independent of hepatic and renal function Metabolised by non-specific plasma esterase-mediated hydrolysis and a nonenzymatic, pH- and temperature-dependent degradation called Hofmann elimination
Cisastracurium	0.15-0.2 mg/kg or 3 x ED95 for 4-7 minutes maintenance dose: 0.01 mg/kg or an infusion at 1-3 mcg/kg/min guided by neuromuscular monitoring	4-7 minutes	35-50 minutes	Volume of distribution is 0.16 L/kg, metabolised through Hofmann elimination
Mivacurium	0.2 mg/kg, or 3 x ED_{95} for 3-4 minutes maintenance dose: 0.1mg/kg or an infusion at 5 to 8 mcg/kg/min guided by neuromuscular monitoring	3-4 minutes	15-20 minutes	Volume of distribution of 0.2 L/kg, metabolized by butyrylcholinesterase and should not be used in patients with butyrylcholinesterase deficiency It can be reversed by neostigmine or edrophonium.

Brull, Sorin; Naguib, Mohamed. "Clinical use of neuromuscular blocking agents in anesthesia". UpToDate. Retrieved 20 April 2020.

Reversal

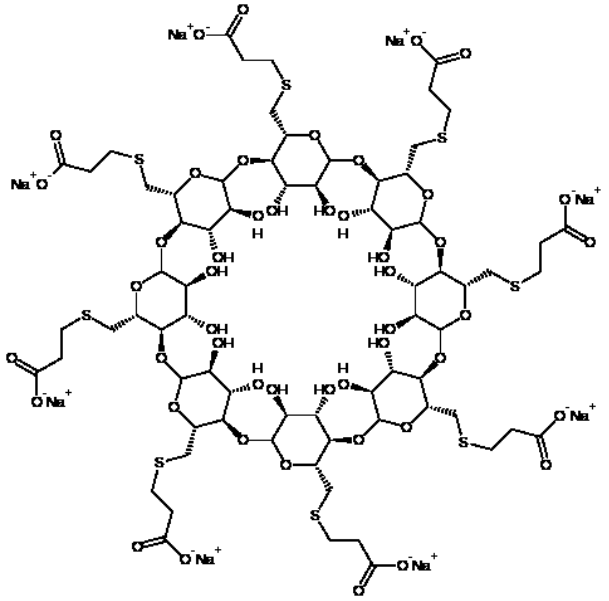
- Acetylcholine esterase inhibitor – neostigmine
  - Increases concentration of Ach at NMJ
- Neostigmine acts at all sites where acetylcholine esterase is present including heart

What effect this might have and how this can be overcome?

Neostigmine

- Dose of neostigmine – 0.05 mg/kg
- In > 50 kg man 2.5 mg
- Given with atropine 0.5 mg

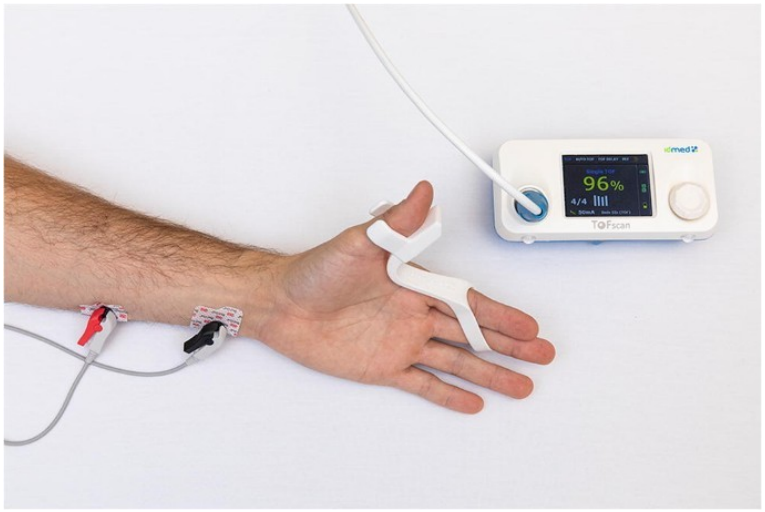
Sugammadex (Bridion)



- medication for the reversal of neuromuscular blockade induced by rocuronium and vecuronium
- the first selective relaxant binding agent (SRBA)
- dose depends on time of use
  - (16 - 4 - 2 mg kg^{-1})
- expensive

Peripheral nerve stimulator

- Check the depth of neuromuscular blockade
  - TOF, PTC ..
- Determine that neuromuscular blockade is reversible
- Check that blockade has been reversed fully (TOFr ≤ 0.9)



SUMMARY – muscle relaxants

- Mechanism of action – via acetylcholine receptor
- Used to facilitate tracheal intubation, mechanical ventilation and surgery
- Depolarizing – Succinylcholine
  - Lots of side effects
- Non depolarizing – Rocuronium, Atracurium, ..
  - Minimal CV and respiratory effects

ANALGESICS

Analgesics

- paracetamol (=acetaminophen), metamizole
- Nonsteroidal anti-inflammatory drugs = NSAIDs
  - (aspirin, ibuprofen, naproxen, indomethacin, diclofenac, meloxicam,..)
- Opioids

- Local anaesthetics
- Antidepressants
- Anti-epileptics
- Ketamine
- Clonidine

1877

Paracetamol = acetaminophen

- classified as a mild analgesic
- does not have significant anti-inflammatory activity
- for severe pain, such as cancer pain and pain after surgery, in combination with opioid pain medication
- is generally safe at recommended doses
- max daily dose for an adult is **4** grams - overdose results in a lengthy, painful illness, acute liver failure and death
- safe during pregnancy and when breas

NSAIDs - effects

- reduces pain
- decreases fever
- prevents blood clots
- decreases inflammation
  - in higher doses

Simple analgesics

1853

- Antipyretic agents found in willow tree and led to development of acetylsalicylic acid

Charles Frédéric Gerhardt

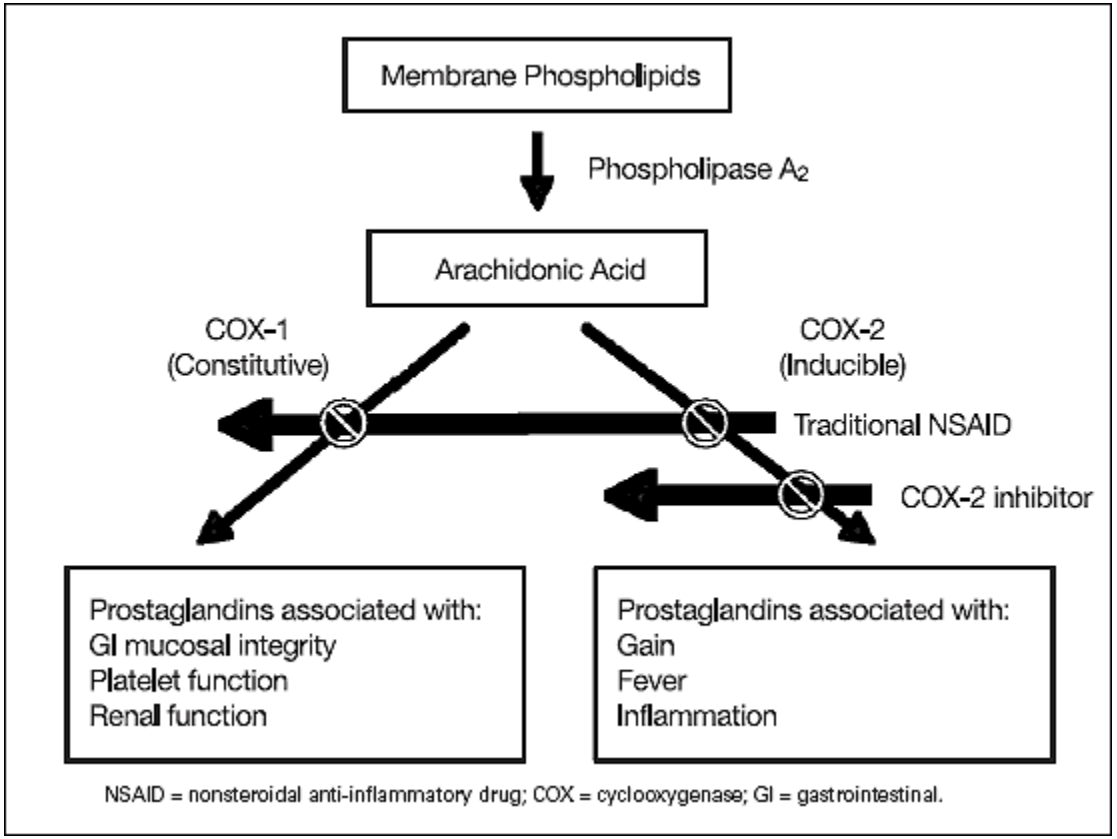
Bayer company had named it "Aspirin"

Acetylsalicylic acid (ASA) = Aspirin

- Anti-inflamatory agent in joint disease
- Cardiovascular - unstable angina
- Antiplatelet drug - prevention of stroke / aMI
- Radiation induced diarrhoea
- Alzheimer's disease

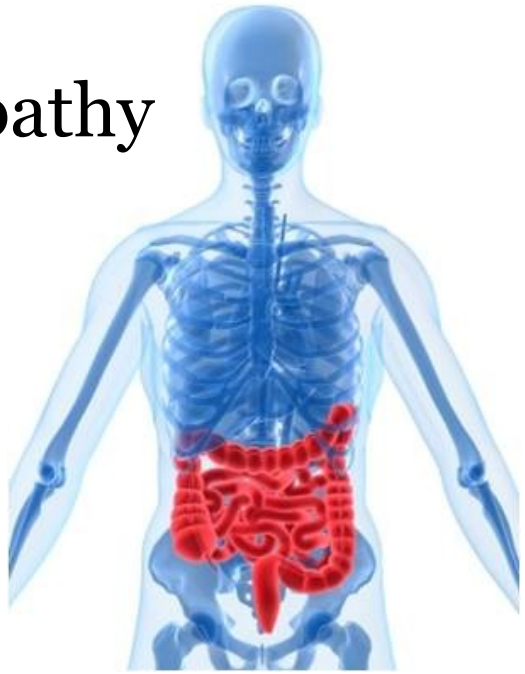
NSAIDs – mechanism of action

- Inhibition of cyclo-oxygenase enzymes (COX-1, COX-2)



NSAIDs – side effects

- Gastric irritation
- Renal dysfunction – analgesic nefropathy
- Antiplatelet function
- Hepatotoxicity
- NSAID sensitive asthma



CAVE: drug interaction – warfarin, lithium

Simple analgesics

	Aspirin	Paracetamol
Chemistry	Acetic acid	Paraaminophenol
Mechanism of action	Inhibition of COX 1	? COX 3 inhib
Metabolism	Estrases in gut wall, liver	Liver
Toxicity	Hepatic/renal inpairment	GI upset
	GI upset	Trombocytopenia
	Rayes syndrome in kids	Liver necrosis
Dose	300 – 900 mg every 6 h	1 g every 6 h
Route of administration	orally	PO/PR/IV

Other NSAIDs

- Ibuprofen – the lowest risk of GI upset
- Indomethacin, Diclofenac – mainly antiinflamatory effect

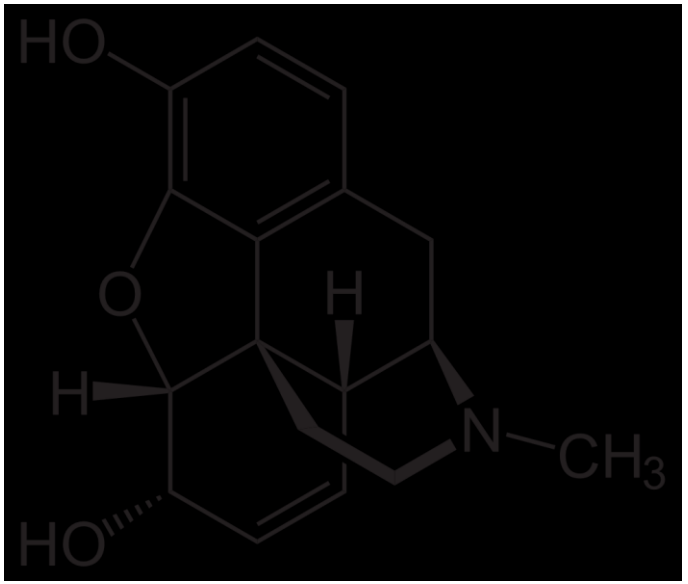
- Aspirin and NSAIDs are not contraindicated for regional anesthesia

SUMMARY – simple analgesics

- Paracetamol
- NSAIDs
- MOA – inhibition of COX
- Renal, gastric, hepatic side effects
- Can trigger NSAID sensitive asthma

Opiods

MORPHEUS
- GREAK GOD OF DREAMS



Morphine

Definitions

- **Opiate** - naturally occuring substance with morphine-like properties; mean a substance derived from opium

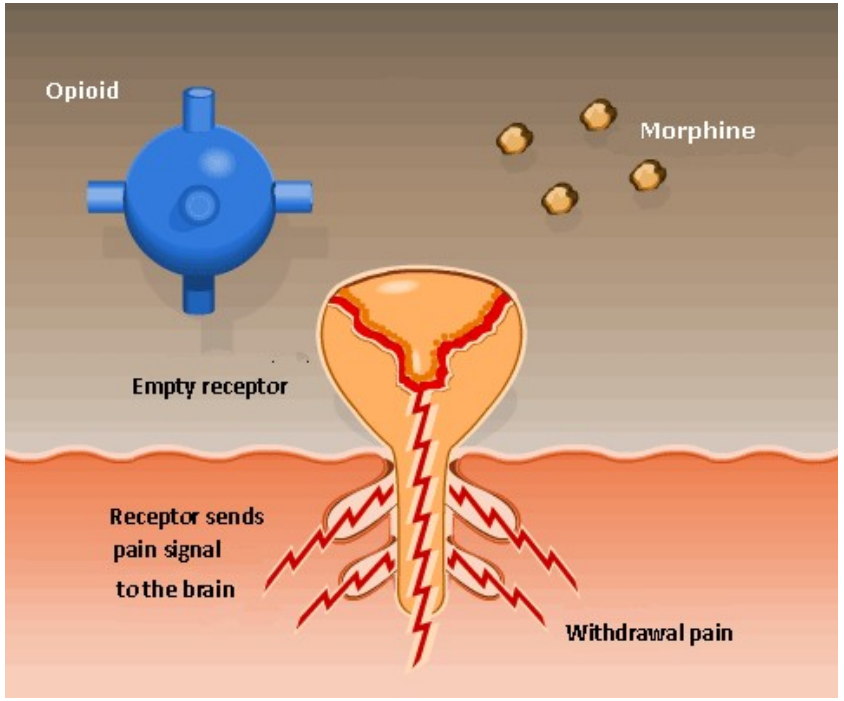
- **Opioid** - all substances, both natural and synthetic, that bind to opioid receptors in the brain (including antagonists)

Narcotic - from greek word ‘numb’

Opium is dried latex obtained from the seed capsules of the opium poppy Papaver somniferum.

Opioids – mechanism of action

- Via opioid receptors - in the central and peripheral nervous system and the gastrointestinal tract
  - μ - receptor
  - κ - receptor
  - δ - receptor



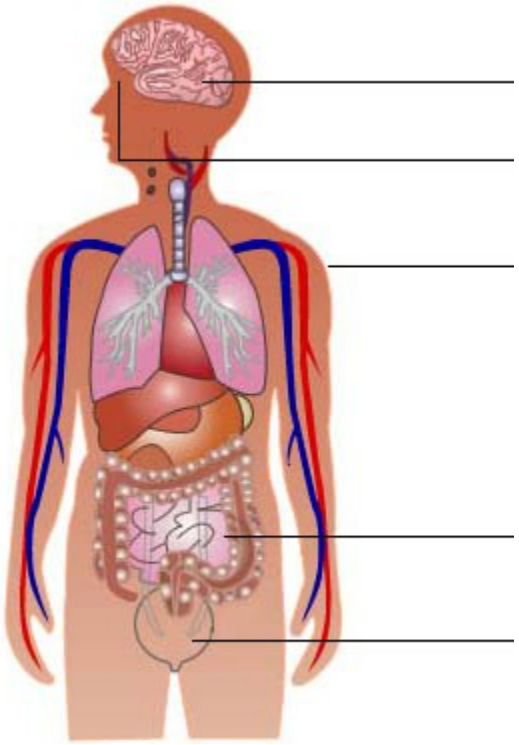
Uses and routes of administration

- Analgesics
- Anti-tussive
- Anti-diarrhoea

- Intravenously
- Intramuscularly
- Oral, Buccal, Rectal
- Transdermal - Patches
- Epidural / Intrathecal

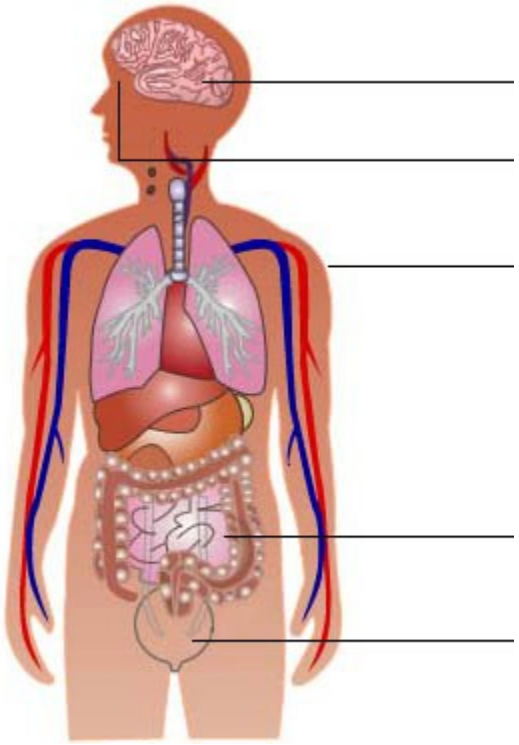
Opioids - effects

- Brain:
  - Analgesia, sedation
  - Respiratory depression / arrest
  - Euphoria and dysphoria
  - Addiction, tolerance
  - Nausea and vomiting
- Eyes
  - Miosis
- Cardiovascular system
  - Hypotension, bradycardia



Opioids - effects

- Respiratory system
  - Anti-tussive effect
- GI tract
  - Spastic immobility
- Skin
  - Pruritus – histamine release
- Bladder
  - Urinary retention



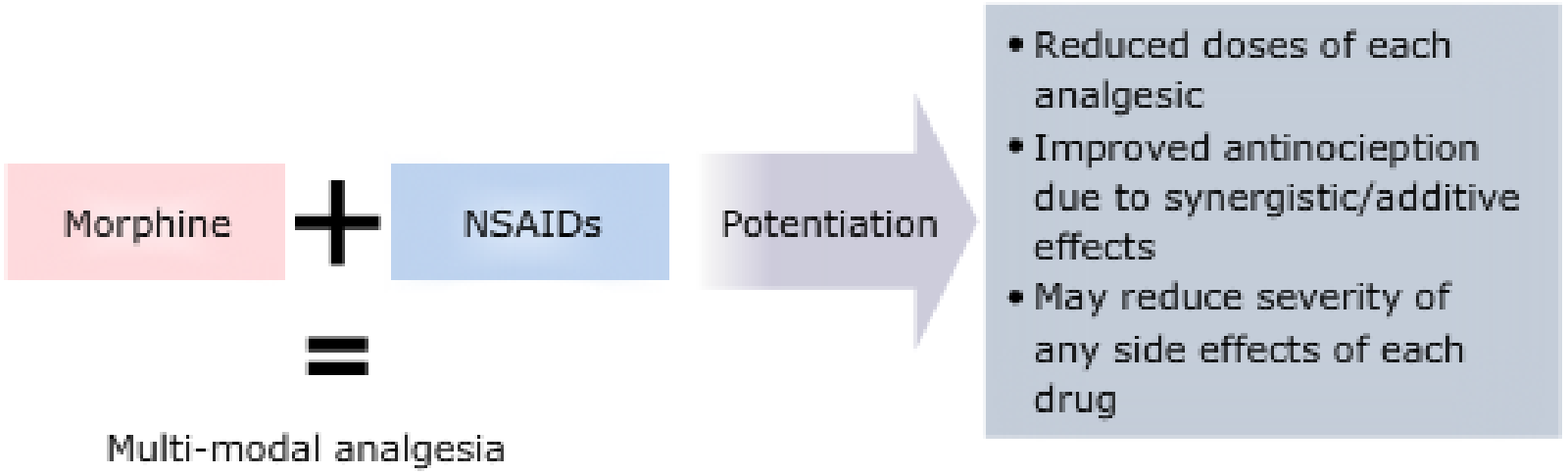
Commonly used opioids

	Dose	Elimination ½ life	Metabolism	Comment
Sufentanyl	0.1 μg/kg	50 min	liver	Faster onset then fentanyl
Fentanyl	1-2 μg/kg	190 min	liver	Neurosurgery, patches
Alfentanyl	5 – 25 μg/kg	100 min	liver	Faster onset then sufentanyl
Remifentanyl	0.05 – 2 μg/kg	10 min	Plasma and tissue esterases	Infusion only, very short context sensit. ½ life

Naloxone

- Pure opioid anatagonist at μ, δ and κ - receptors
- Used in opioid overdose as an **antidote**
- Dose : 1- 4 μg/kg
- Duration of action 30 – 40 min
- ! Often shorter then duration of action of opioid, need for repeated doses

Multimodal analgesia



SUMMARY – opioids

- Morphine, Fentanyl, Sufentanyl, Alfentanyl
- MOA – via opioid receptors
- Used for analgesia, anti–tussive, anti–diarrhoea
- Side effects : respir. depression, tolerance, constipation, nausea + vomiting
- Opioid overdose reversal – Naloxone
- Multimodal analgesia – simple analgesics + opioids

SUMMARY

- Triad of anaesthesia
  - Analgesia
  - Anaesthesia
  - Muscle relaxation

- Choice depends on
  - Patient factors
  - Type of surgery
  - Whether the surgery is elective or emergency

Questions ?