PHARMACOLOGY OF ANAESTHETICS

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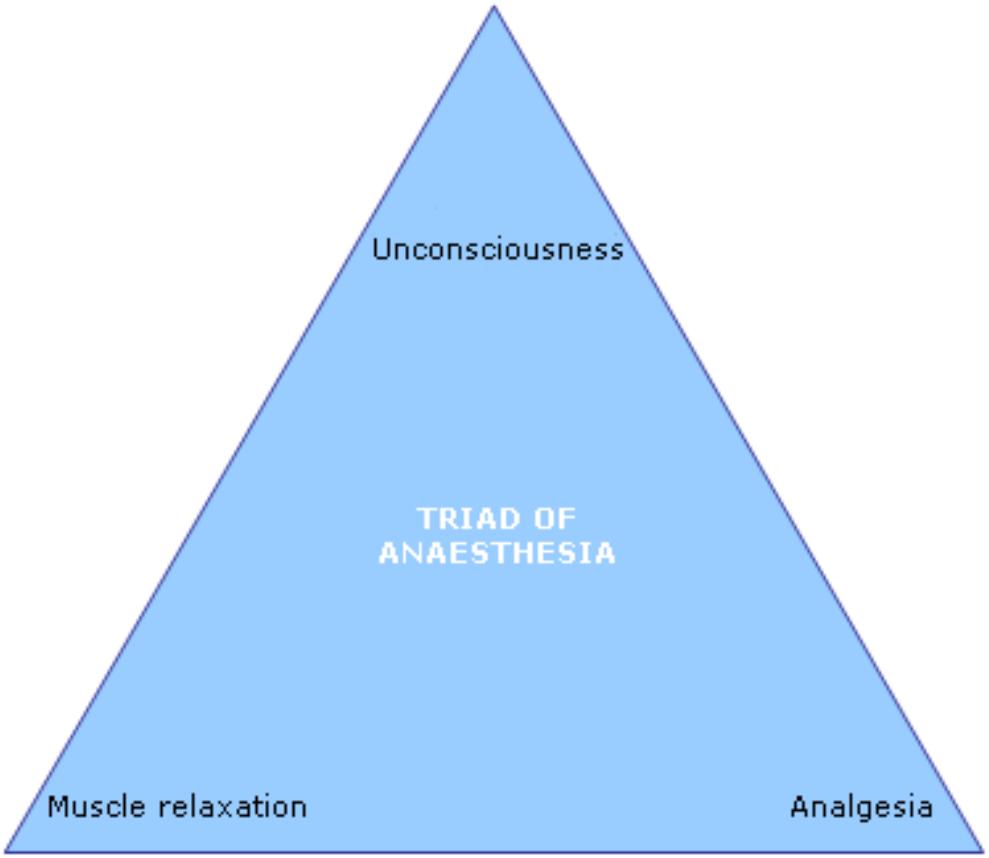
AIMS OF ANAESTHESIA



Triad of anaesthesia

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

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

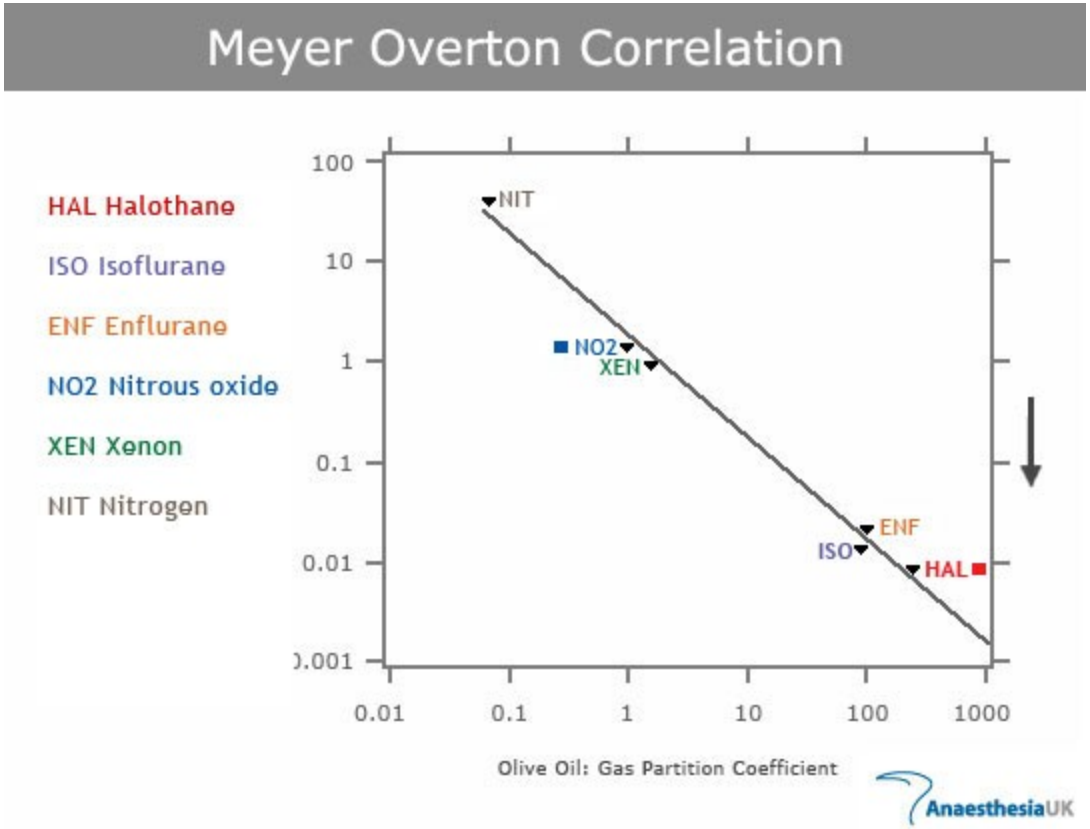
- Onset of anaesthesia within one arm – brain circulation time – 30 sec
- Effect site ➡ brain
  - Propofol
  - Thiopentale
  - Etomidate

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

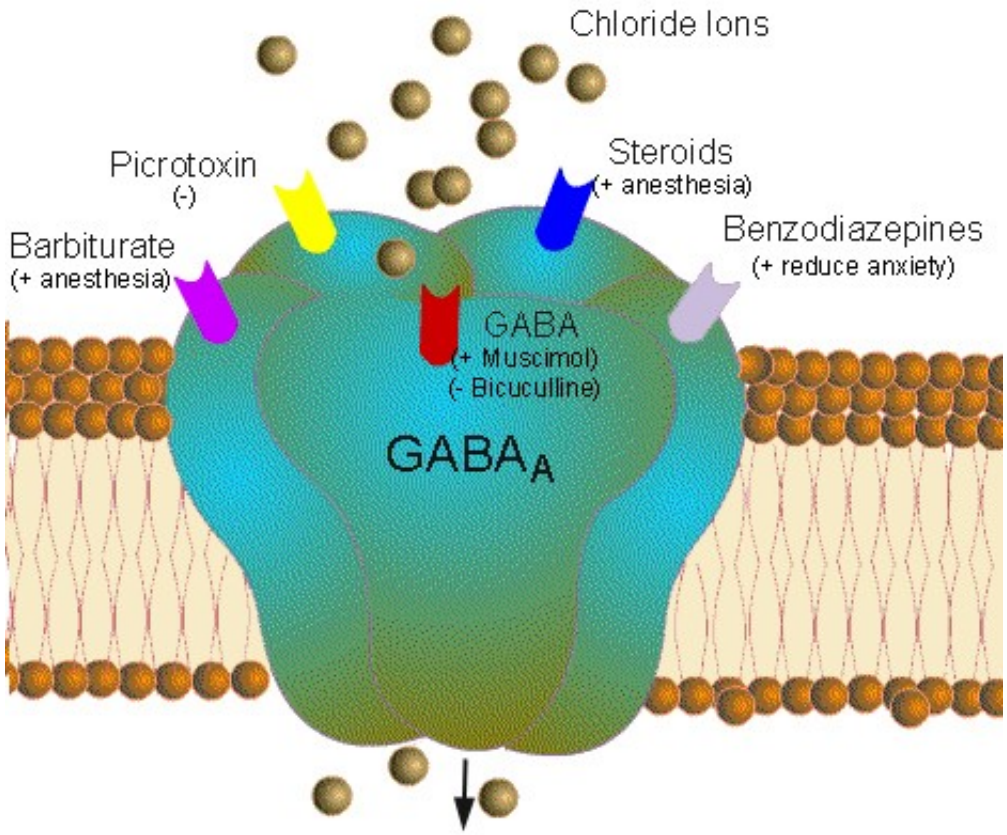


- Linear correlation between the lipid solubility and potency

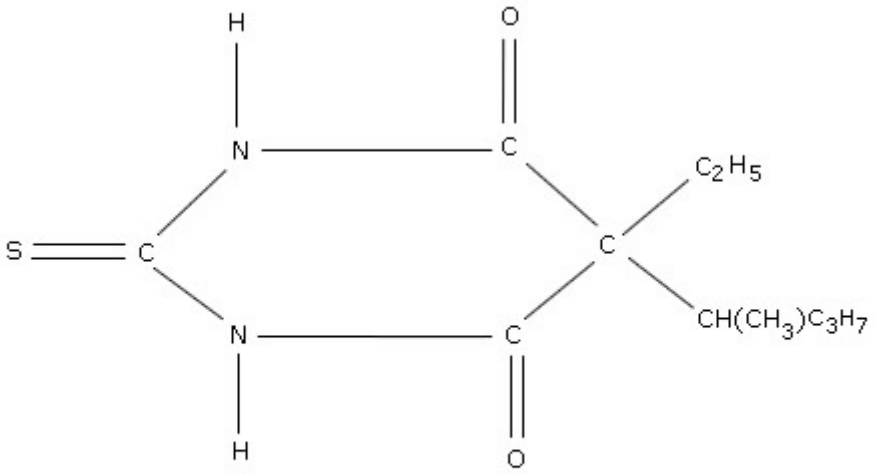
Molecular theories

- 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



Thiopentale

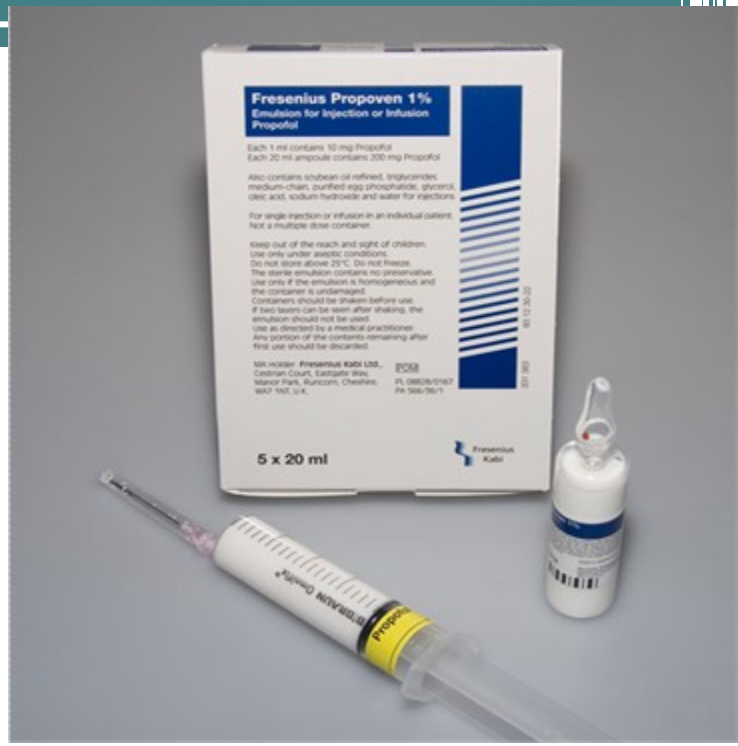


- Barbiturate
- **Dose** 3-7 mg/kg
- **Effects** : hypnosis, atiepileptic, antanalgesic
- **Side effects**
  - CVS: myocardiac depression, ↓CO
  - Reduction in MV, apnea

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

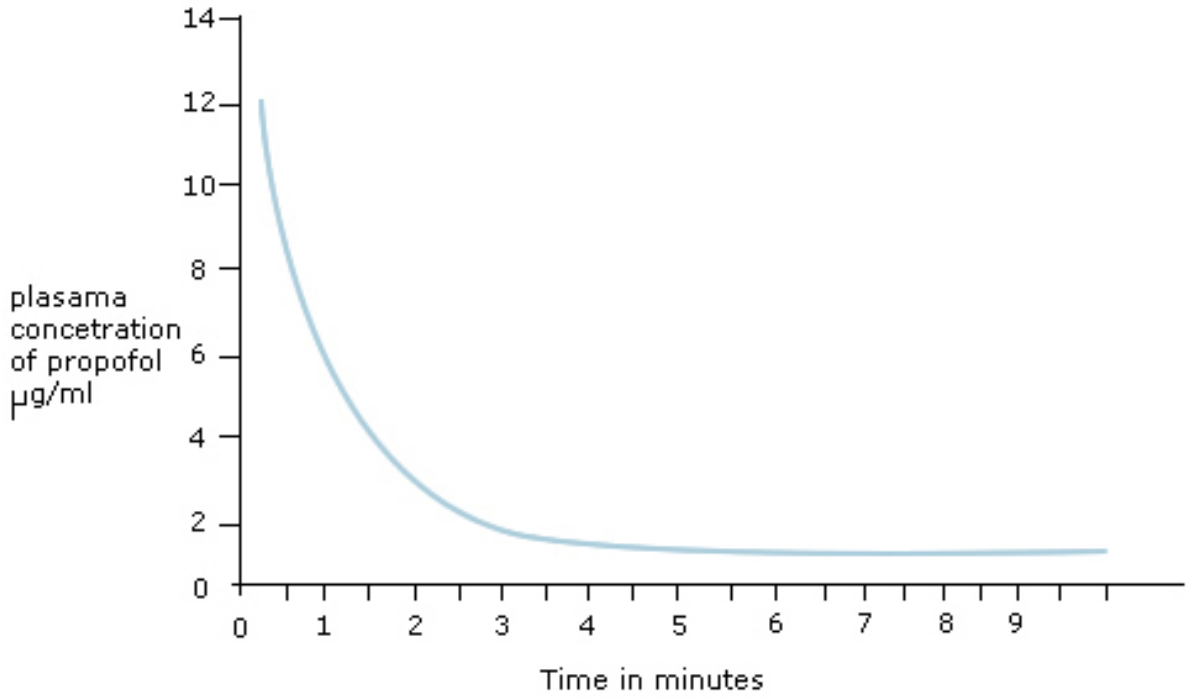
Etomidate

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

- **Relative Contraindications**
  - Porphyria

Pharmakokinetics

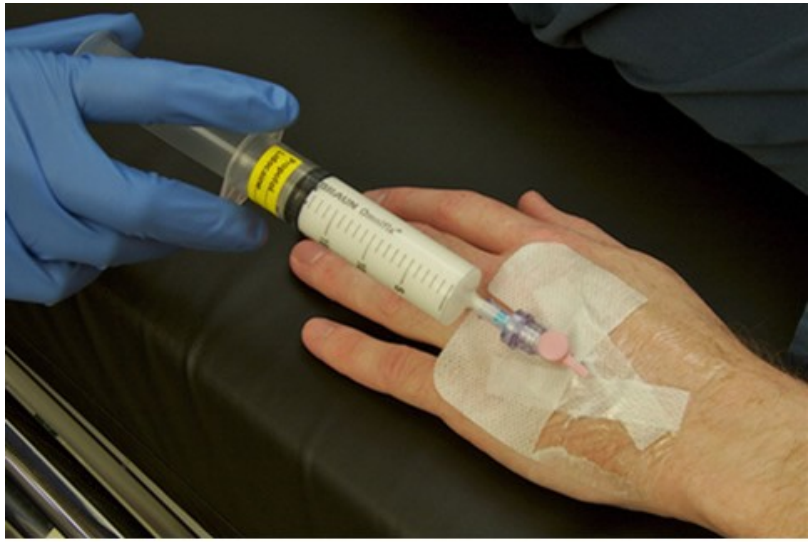
- Recovery from single bolus 5-10 min



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



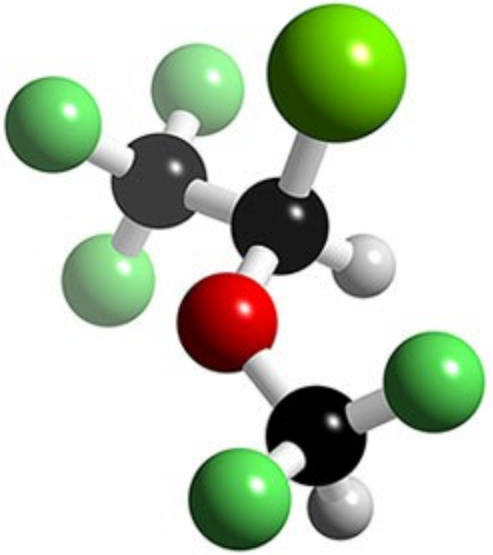
SUMMARY – IV anaesthetics

- Mechanism of action – via receptors
- Used for anaesthesia and sedation
- Used for induction
- Propofol used for maintenance as well
- Thiopentale, propofol, etomidate
- All cause CV and respiratory depression

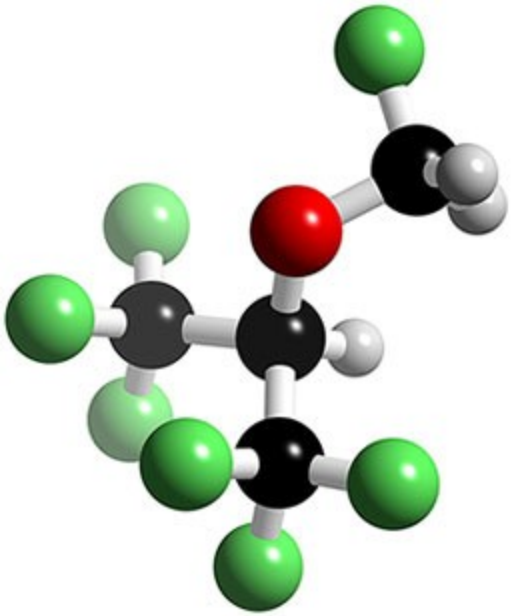
INHALATIONAL ANAESTETICS

Anaesthetic gases

- Isoflurane
- Sevoflurane



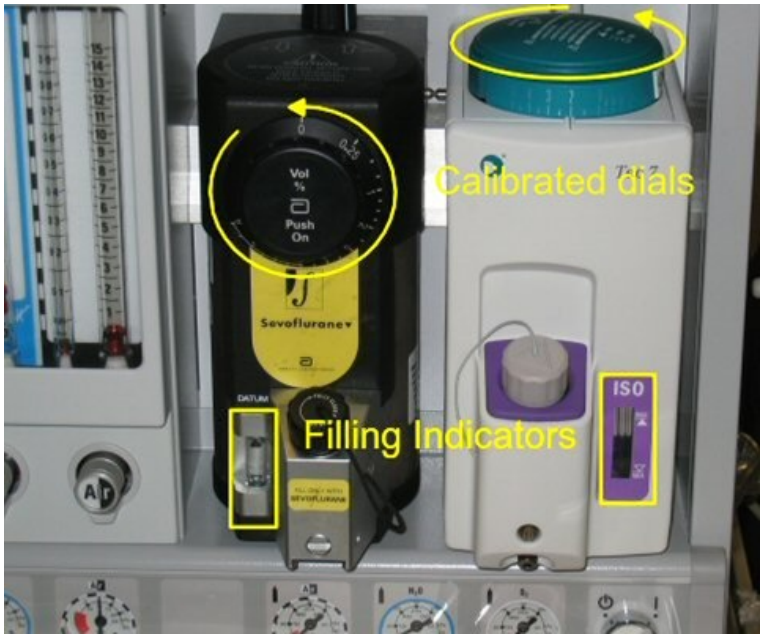
- Halothane
- Enflurane
- Desflurane



- 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 %

Potency

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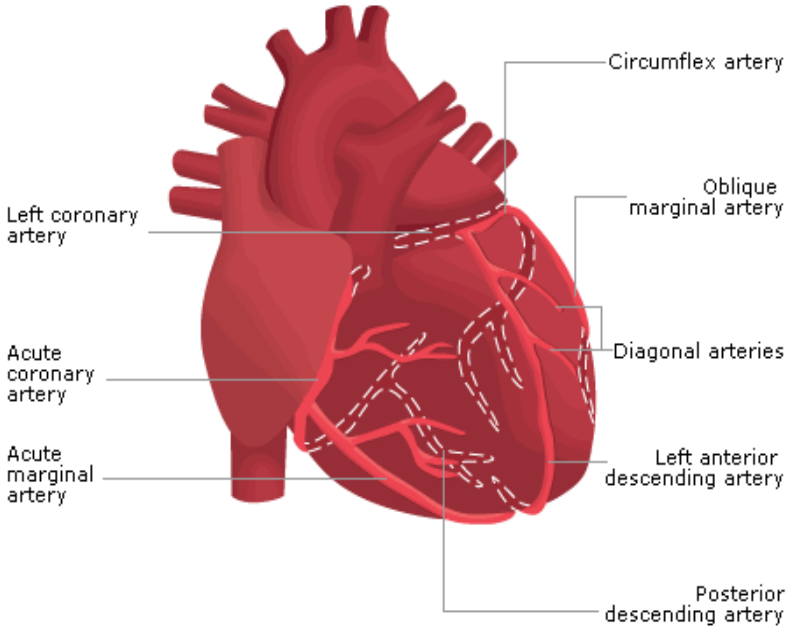
- Sevoflurane MAC 1.8 %
- **Isoflurane MAC 1.17 %**

Respiratory and cardiovascular effects

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



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

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

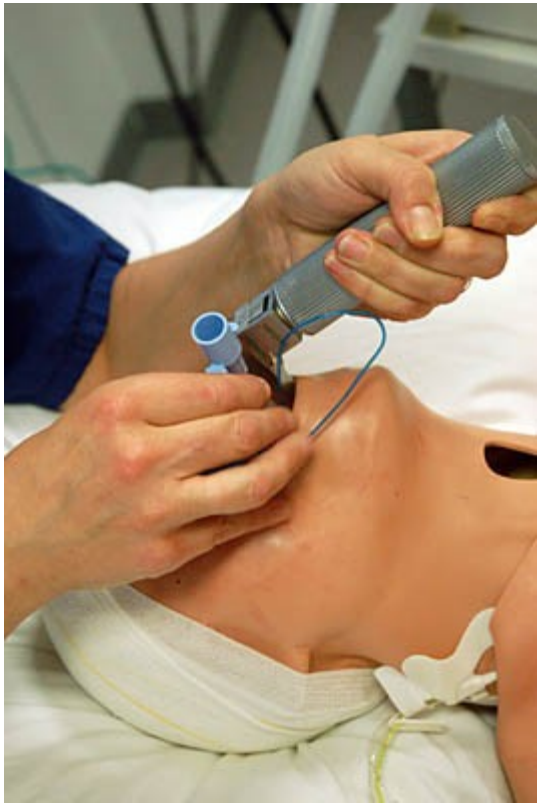
NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents

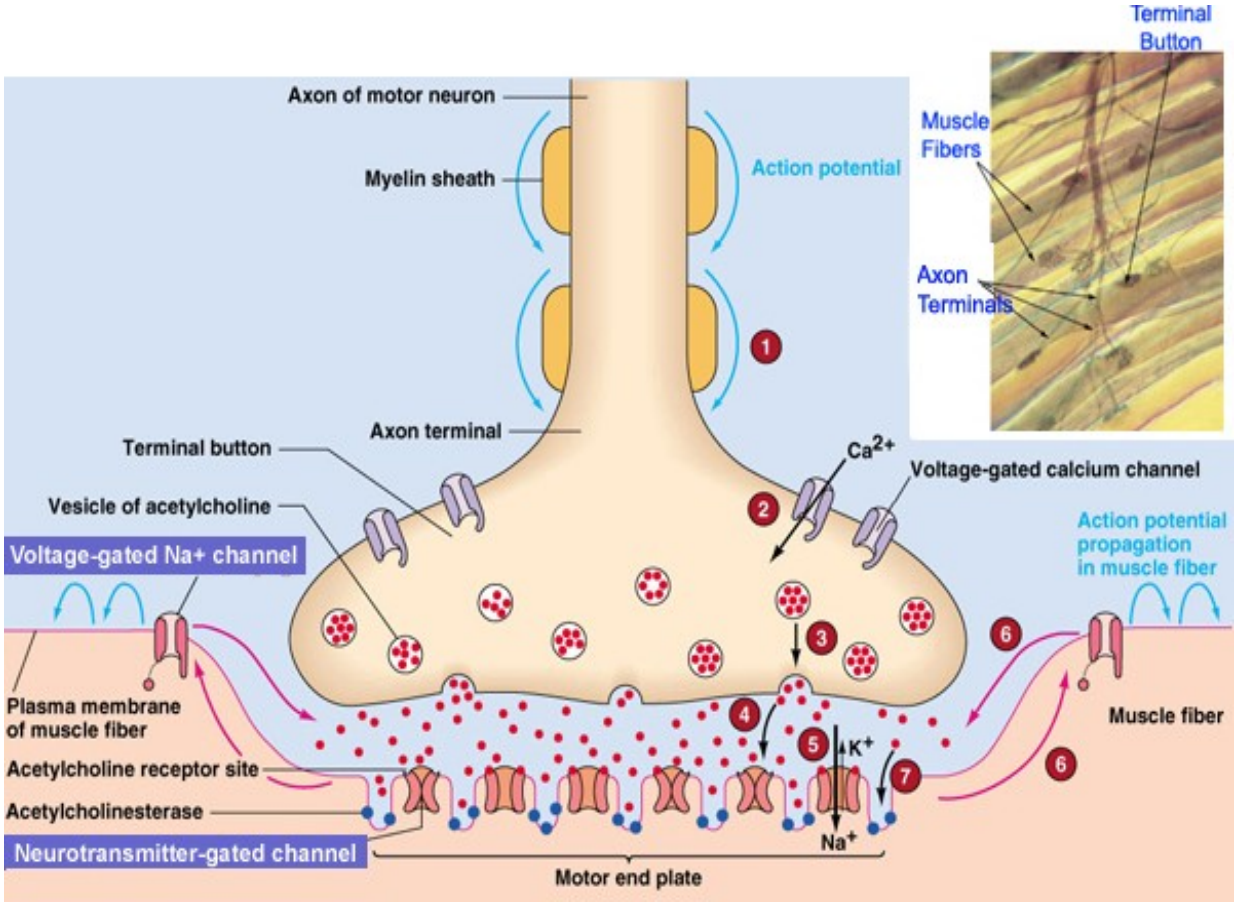
- Exclusively used in anaesthesia and intensive care
- Two classes
  - Depolarizing
    - succinylcholine
  - Non depolarizing
    - Vecuronium - aminosteroid
    - Atracurium - benzylisoquinolinium

Use of NMBs

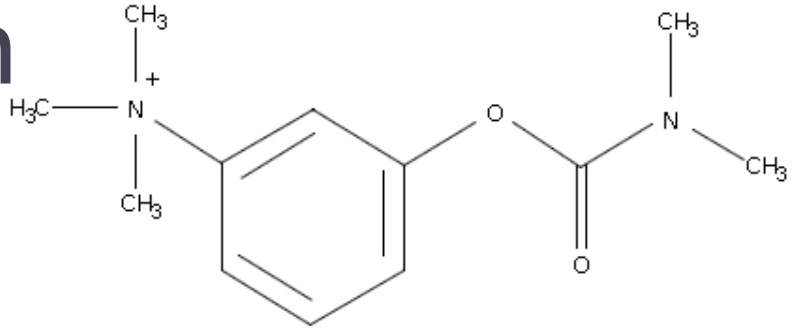
- Tracheal intubation
- Surgery where muscle relaxation is essential
- Mechanical ventilation



Neuromuscular junction



Mechanism of action



- Depolarizing
  - Structurally related to Ach
  - First activating muscle fibres, then preventing further response

- Non depolarizing
  - Compete with Ach at nicotinic receptor at the neuromuscular junction

Choice for tracheal intubation

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

Intubating doses

Succinylcholine	1 – 2 mg/kg
Vecuronium	0.1 mg/kg
Atracurium	0.5 mg/kg

To maintain paralysis

- Non depolarizing muscle relaxants

Succinylcholine	No
Vecuronium	0.02 – 0.03 mg/kg
Atracurium	0.1 – 0.2 mg/kg

Succinylcholine

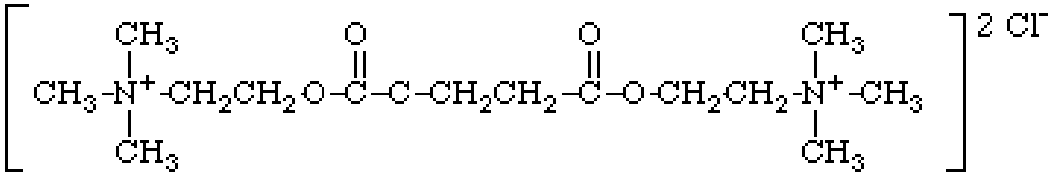
- Patient related contraindications
  - Malignant hyperpyrexia
  - Anaphylaxis to SCh
  - Succinycholine apnea
- Clinical contraindications
  - Denervation injury
  - Penetrating eye injury

Succinylcholine - other adverse effects

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

Succinylcholine pharmacokinetics

- Duration of action : 3 - 5 min
- Metabolism – plasma cholinesterase
  - Cave: suxamethonium apnea



Non depolarizing muscle relaxants

- Choice of NMBs
  - Personal preference
  - Atracurium better in renal or hepatic failure
  - Avoid atracurium in asthmatic patients

Reversal

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

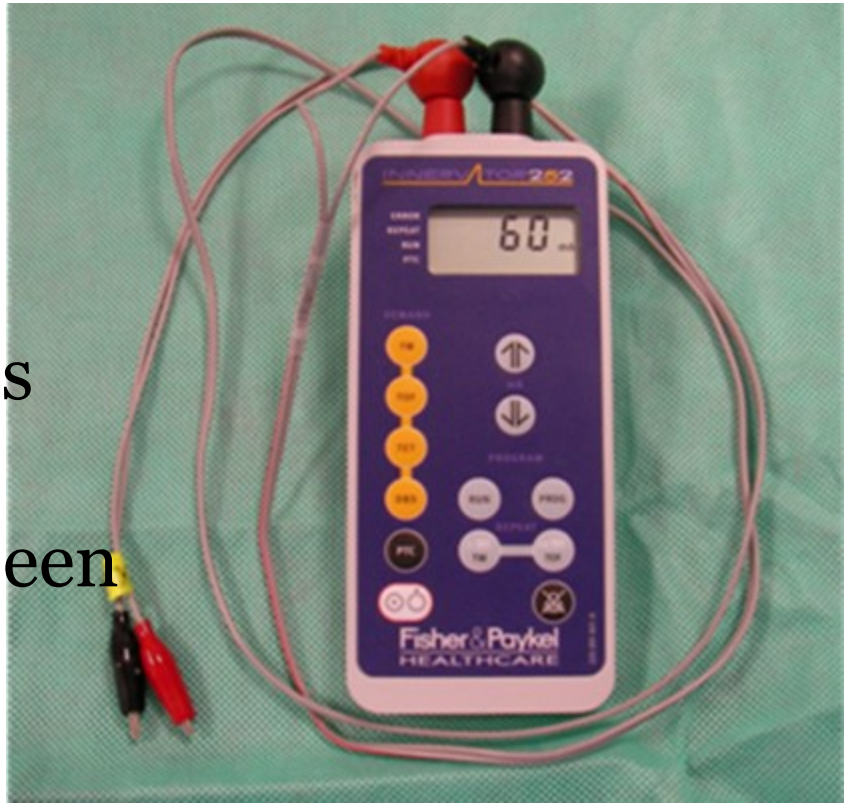
What effect this might have and how this can be overcome?

Neostigmine

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

Peripheral nerve stimulator

- Check the depth of neuromuscular blockade
- Determine that neuromuscular blockade is reversible
- Check that blockade has been reversed safisfactorily



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 – Vecuronium, Atracurium
  - Minimal CV and Resp. effects

ANALGESICS

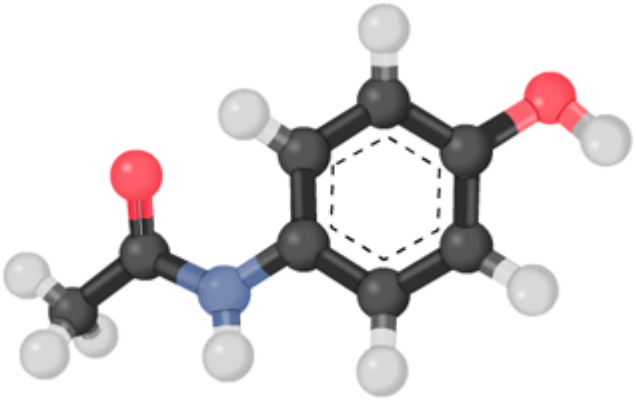
Analgesics

- Paracetamol, aspirin
- Other Non Steroid Anti Inflamatory Drugs
- Opioids

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

NSAIDs - effects

- Antipyretic
- Anti-inflamatory
- Analgesic



Simple analgesics

1899

- Antipyretic agents found in white willow bark and led to development of aspirin

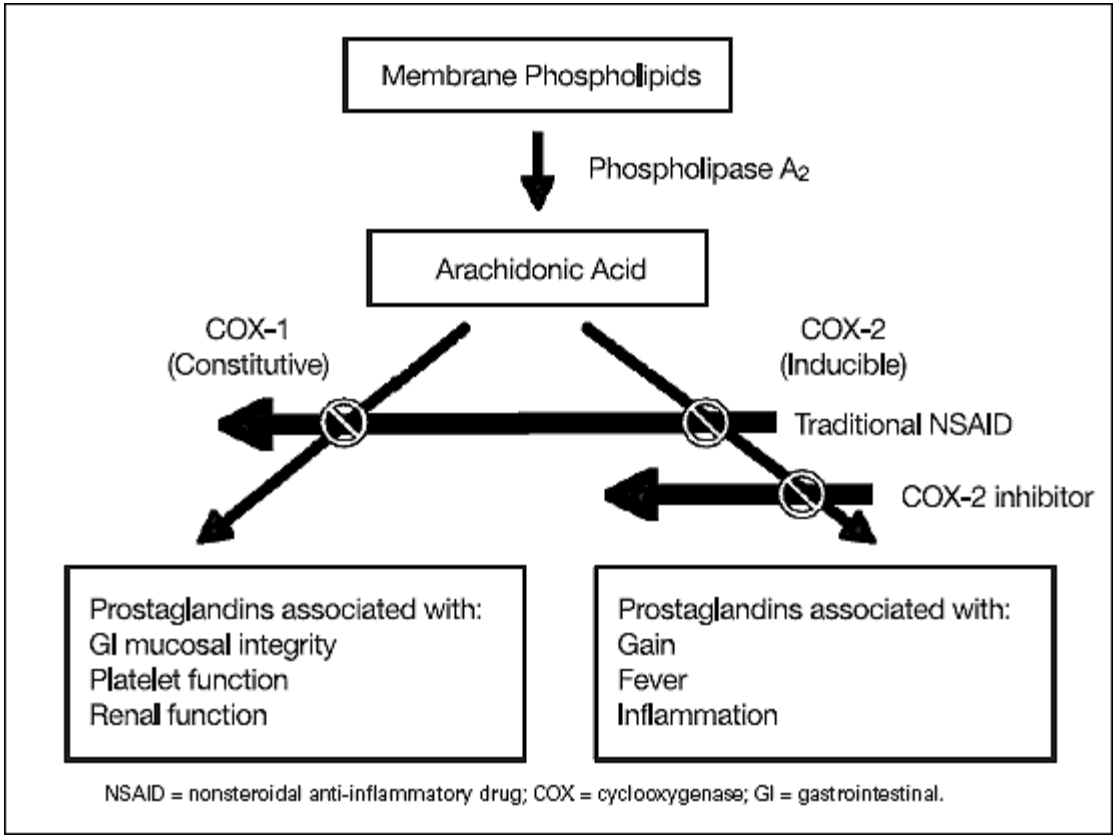
Aspirin

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

What else is aspirin used for ?

NSAID – mechanism of action

- Inhibition of cyclo-oxigenase



NSAID – side effects

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

- 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
- Metamizole –Novalgin
- Aspirin and NSAIDs are not contraindicated for regional anesthesia

SUMMARY – simple analgesics

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

Opiods

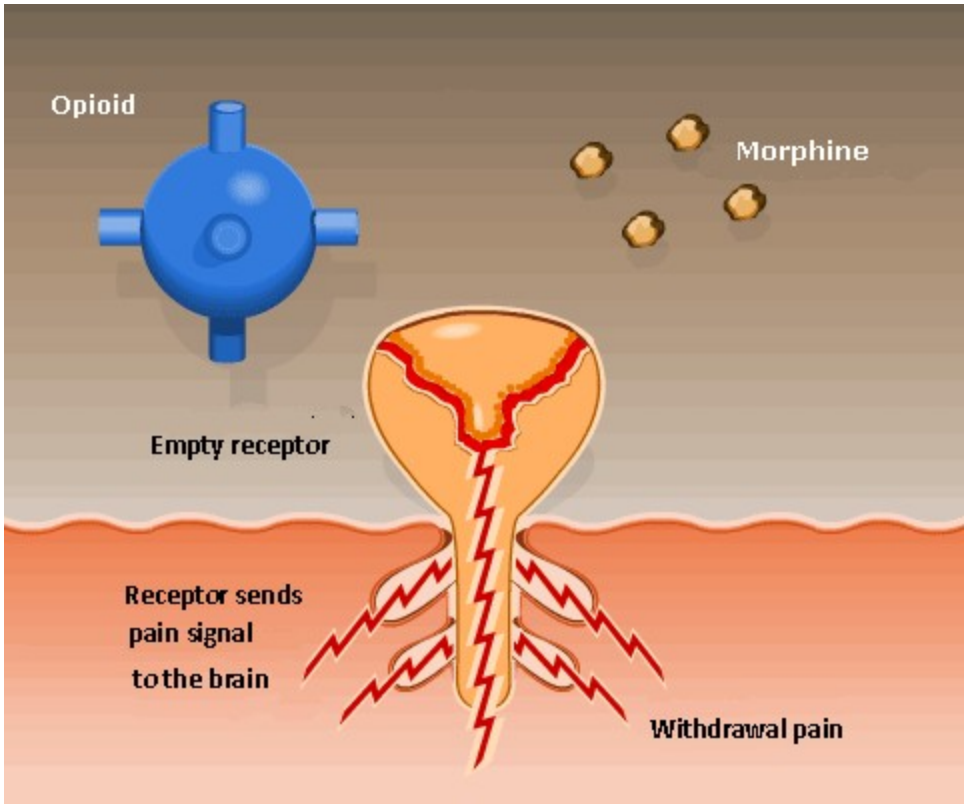
- MORPHEUS- GREAK GOD OF DREAMS

Definitions

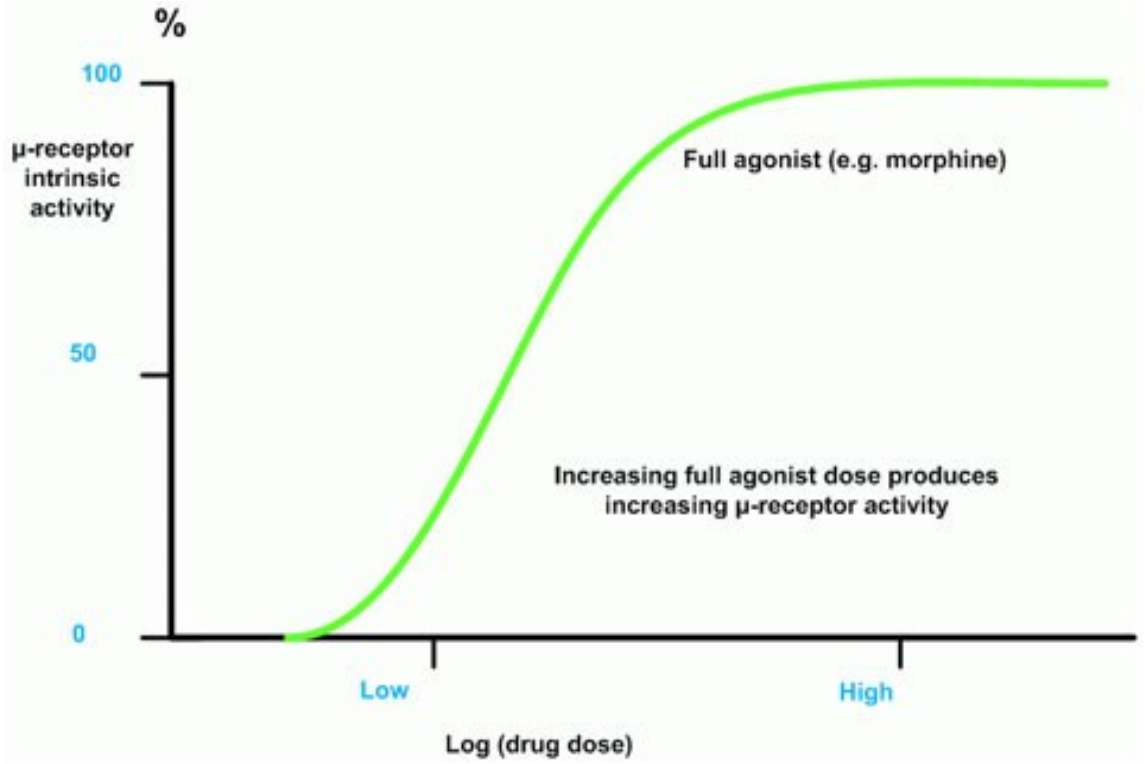
- **Opiate** : naturally occuring substance with morphine-like properties
- **Opioid** – synthetic substance
- **Narcotic** – from greek word ‘ numb’

Opioids – mechanism of action

- Via opioid receptors
  - μ - receptor
  - κ - receptor
  - δ - receptor



Opioids - dose – response curve



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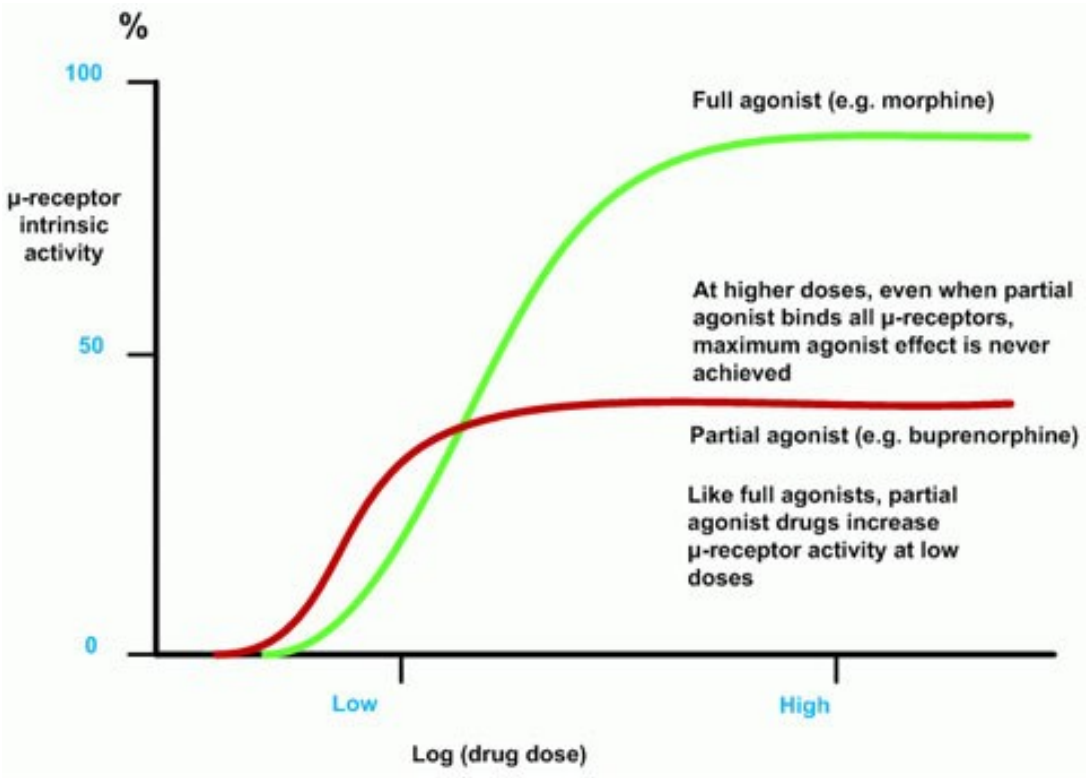


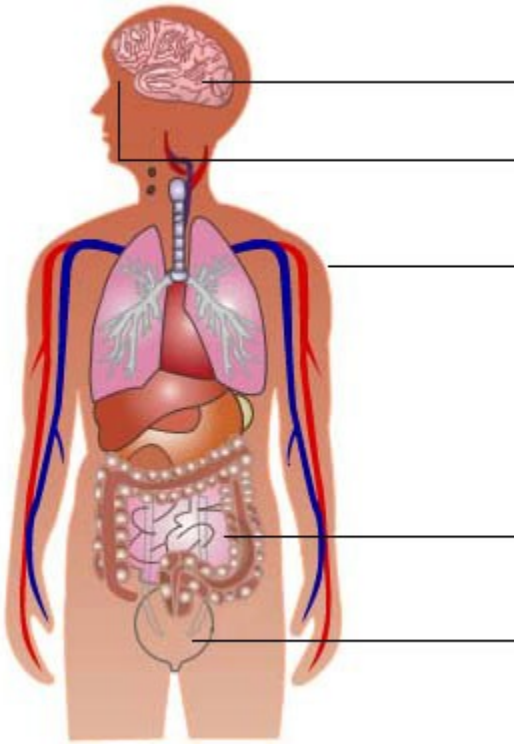
Uses and routes of administration

- Analgesics
- Anti - tussive
- Anti – diarrhoea

- Intravenously
- Intramuscularly
- Oral, Buccal, rectal
- Transdermal - Patches
- Epidural/intrathecal

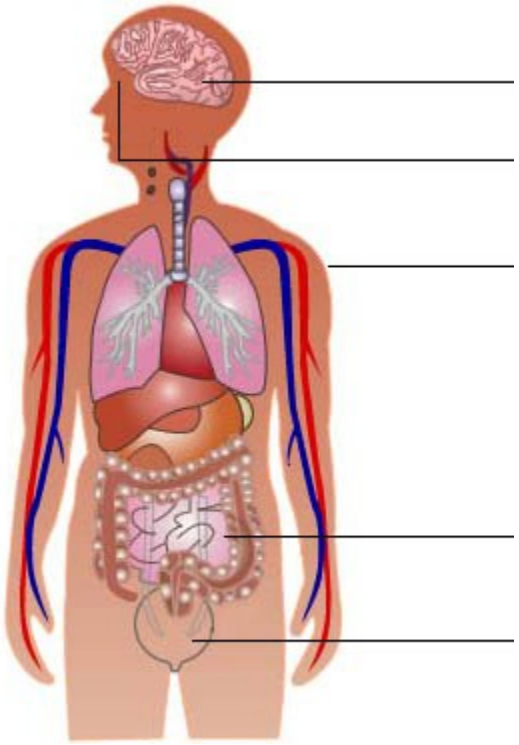
Opioids - effects

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



Opioids - effects

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



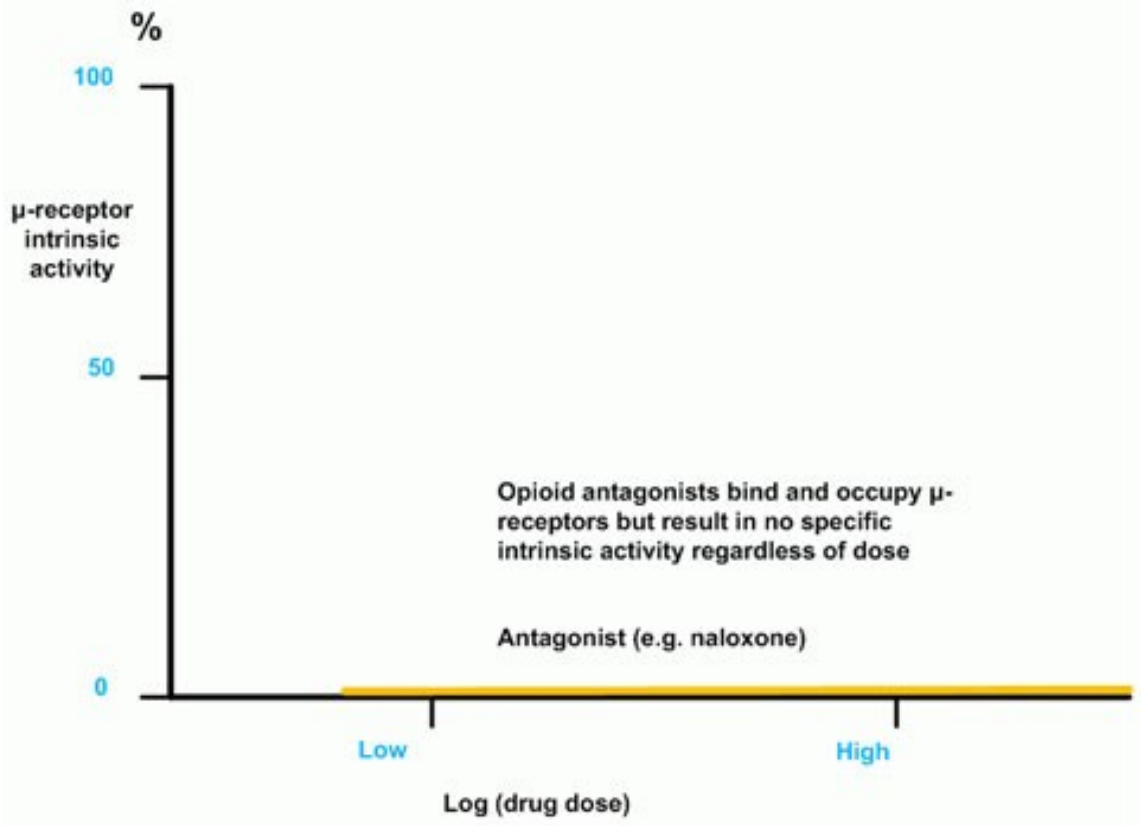
Commonly used opioids

	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

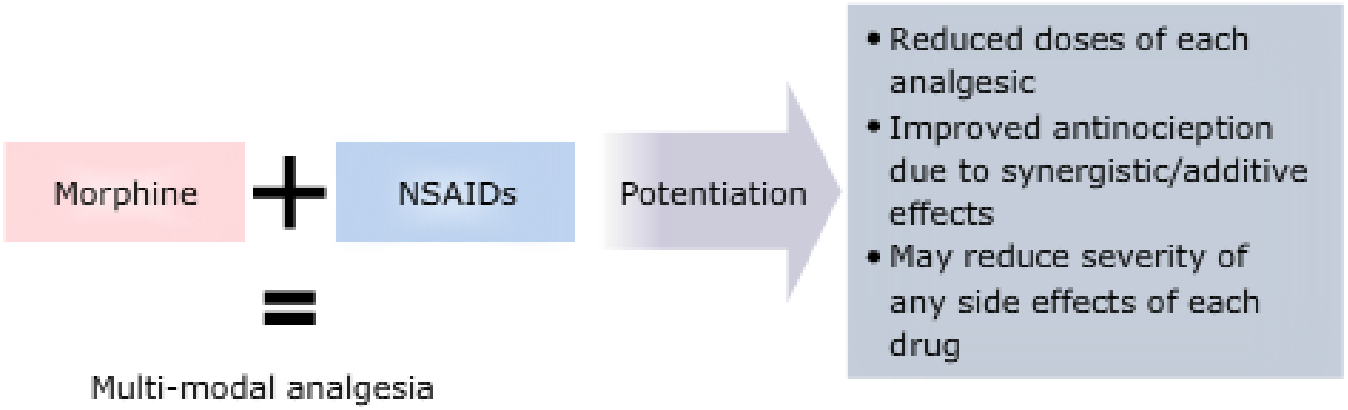
Naloxone

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

Naloxone – dose – response curve



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 ?