ANAESTHESIA- DAY 2

- PHARMACOLOGY OF ANAESTHETIC DRUGS
- REGIONAL ANAESTHESIA
- PERIPHERAL BLOCKS
INHALATIONAL ANAESTHETICS

Classification:

Now a days used –

Halothane
Isoflurane
New Agent
Desflurane
sevoflurane
Obsolete
Enflurane
Ether
Methoxyflurane
Triclae
Chloroform
MOA of inhaled anaesthesia

- No single site of action.
- RAS, cerebral cortex, cuneate nucleus, olfactory cortex, & hippocampus—probable sites
- Depress excitatory transmission in the spinal cord, particularly @ level of the dorsal horn (pain transmission).—GABA receptor
- Unconsciousness & amnesia → cortical anesthetic action,
- Analgesia subcortical.
- Unitary hypothesis
- Meyer–Overton rule.
- Critical volume hypothesis
- Fluidization theory of anesthesia and the lateral phase separation theory
- Glycine receptor $\alpha_1$-subunit, -- extensively investigated
• Potency of inhalational agents

• Anesthetic potency a lipid solubility (Mever Overton rule)

• MINIMUM ALVEOLAR CONCENTRATION

• Best estimate for the potency of inhalational anaesthetics is MAC

• MAC minimum alveolar concentration (at 1 atm.) of an agent required to produce immobility in 50% of subjects exposed to noxious stimuli i.e. skin incision in human & tail clamping in animals.
<table>
<thead>
<tr>
<th>Substance</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Chloroform</td>
<td>0.8%</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>0.16%</td>
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<tr>
<td>Ether</td>
<td>1.92%</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.74%</td>
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<tr>
<td>Isoflurane</td>
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<tr>
<td>Cyclopropane</td>
<td>9.2%</td>
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<td>Sevoflurane</td>
<td>2.05%</td>
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<tr>
<td>Enflurene</td>
<td>1.68%</td>
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<tr>
<td>$N_2O$</td>
<td>104%</td>
</tr>
<tr>
<td>Trieline</td>
<td>0.2%</td>
</tr>
<tr>
<td>Desflurane</td>
<td>6%</td>
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</tbody>
</table>
FACTORS EFFECTING MAC

↓ing-age (max MAC is at 6 months of age), hypothermia, hyperthermia up to 42° c
Pregnancy, hypoxia and hypercarbia (only severe), anemia (severe), iv agents, Local anaesthetics, hyponatremia, hypercalcemia and hypermagnesemia, acute alcohol intoxication

↑ing-hyperthermia > 42° c, ↑barometric pressure, chronic alcohol, hypernatremia

No effect- sex, thyroid disorder
<table>
<thead>
<tr>
<th>Compound</th>
<th>Blood Gas Partition Coefficient</th>
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<tbody>
<tr>
<td>$N_2O$</td>
<td>0.47</td>
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<tr>
<td>Cyclopropane</td>
<td>0.44</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.8</td>
</tr>
<tr>
<td>Xenon</td>
<td>0.14 - earliest induction and recovery</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.42 - earliest induction and recovery among the agent</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.69</td>
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<tr>
<td>Ether</td>
<td>12</td>
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<tr>
<td>Metoxyflurane</td>
<td>15- slowest</td>
</tr>
<tr>
<td>Trieline</td>
<td>9</td>
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<tr>
<td>Isoflurane</td>
<td>1.38</td>
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<tr>
<td>Halothane</td>
<td>2.4 slowest among now a days agents used</td>
</tr>
<tr>
<td>Chloroform</td>
<td>8</td>
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</tbody>
</table>
CONCENTRATION EFFECT AUGMENTED INFLOW EFFECT,

This is seen if $N_2O$ along with another potent anesthetic is given. With the removal of $N_2O$ from lung, total volume of lung $\downarrow$ leading to $\uparrow$ cond. of remaining gas in the lung (Concentration effect).

SECOND GAS EFFECT

With the next inspiration of same mixture $N_2O$ & other agent conc is further $\uparrow$ ed. this effect i.e. one gas effecting the conc. of other is known as second gas effect.

DIFFUSION HYPOXIA (FINK)

At the end when $N_2O$ is discontinued alveolar to venous gradient reverses causing to high conc. of $N_2O$ in alveoli displacing $O_2$ this is called as diffusion hypoxia. It is seen during first 5-10 minutes after discontinuation of nitrous oxide.
A 1% Second gas

B 1% Second gas

Inspiration 31.7%

Containing 80% N₂O 19% O₂ and 1% second gas

50% of N₂O taken up

80% N₂O

19% O₂

0.4% Second gas

7.6%

32%

N₂O

O₂

N₂O

O₂

ALVEOLAR CAPILLARY

ALVEOLUS

HIGH PARTIAL PRESSURE

LOW PARTIAL PRESSURE

INDUCTION OF INHALATION SEDATION

BLOOD FLOW

RECOVERY FROM INHALATION SEDATION
EFFECT OF INHALATIONAL AGENTS ON SYSTEMS

Bronchial muscles —→ All are bronchodilators. Maximum in non asthmatic by sevoflurane & halothane.

Pulmonary vascular resistance - All are pulmonary vasodilators except $N_2O$ which is constrictor.

Mucociliary function - All agents ↓ the ciliary movement except ether.

Respiration: All agents ↓ tidal volume but ↑ frequency initially but with higher doses both tidal volume and frequency decreases.

Sequence for respiratory depression by inhalational agents in decreasing order:

Enflurane > desflurane > isoflurane > sevoflurane > halothane
EFFECTS ON CVS

- All agent ↓ SVR (max. with isoflurane)
- All ↓ CO (Enflurane > halothane > sevoflurane > isoflurane)

Therefore isoflurane is agent of choice for cardiac patients

EFFECT ON CNS:

- All ↓ cerebral metabolic rate (CMR) and O2 consumption of brain at high doses (isoflurane at clinical doses)
- All increases ICP (enflurane > halothane > sevoflurane > isoflurane = desflurane (<6%))
EFFECT ON LIVER: -
Hepatotoxic are
• Halothane
• Chloroform
• Methoxyflurane

Hepatic blood flow: All decreases total blood flow to liver. Maximum with halothane and minimum with sevoflurane.

RENAL SYSTEM:-
Nephrotoxicity is because of fluoride (fluorinated to make them non.inflammable)
-renal threshold is 50 $\text{\textmu M}$

• Methoxyflurane -50-70
• Sevoflurane- 30-50
• Enflurane-20-25
• Isoflurane-4-8
• Halothane-only under anaerobic conditions  

Desflurane - nil
• **Uterus:** all agents relaxes uterus equally.

• **Muscular system:** centrally acting muscle relaxants (except nitrous), i requirement of muscle relaxants by 30%.
  - (Desflurane>sevoflurane>isoflurane> halothane)

• **Metabolic:** hyperglycemia by choloroform/ cyclopropane, ether and desflurance>6%

• **Ocular:** All decrease I.O.P.

• **Analgesia:** all agents now days are not analgesics

• **Metabolism**
  - All undergo oxidation ,except halothane which also undergoes reduction
  - max. metabolism- methoxyflurane and min. - desflurane,
  - \( N_2O \) dose not metabolized in human tissues
AGENTS IN COMMON USE: \( N_2O \)

- Cylinder color is blue
- Prepared by heating ammonium nitrate
- Stored in cylinder as liquid (since critical temp. - 36.5°C)

Physical properties
- Colorless
- Sweet smelling (Also K/a laughing gas)
- Non-irritating
- Not metabolized in body
- Mostly eliminated unchanged through lungs (95%) & 5% through skin.
- 15 times more soluble than O2 and 35 times more soluble than nitrogen
- MAC - 104%
- Blood gas coefficient - 0.47
- Non-inflammable, non explosive.
- Impurities -> Nitric oxide & Nitrogen dioxide (can cause methemoglobinemia, larynospasm)
ANESTHETIC PROPERTIES

- Not a complete anesthetic
- Acts as a carrier gas to other agents
- Given in mixture with O2 (33%) + N₂O (66%)
- Good analgesic
- Not a muscle relaxant
- No effect on CVS & resp. system (negligible)

So N₂O is C/I in - pneumothorax
- Pneumoperitoneum
- Pneumoencaphalum
& best avoided for - Tympanoplasty (can displace graft)
- Surgeries with increased possibility of air embolism like posterior fossa surgery,
• Laparoscopies
  - Intestinal obstruction (therefore contra indicated in diaphragmatic hernia)
  micro laryngeal surgeries – cuff size increase

• Nitrous oxide by supporting fire can cause burns in presence of laser

• 2. Following prolonged administration it can impair DNA synthesis causing bone marrow aplasia and Sub acute degeneration of spinal cord( impaired myelin formation)

• Inactivates vit B12 component (cobalamin) so can cause megaloblastic anemia if used for > 6 hrs.

• Teratogenic effect - observed only in animals

• 5. Reacts with O2 in atmosphere to form NO - destructive to ozone
• **Xenon**: Inert gas (so no systemic side effects), non inflammable, good analgesic
  
  - Lowest blood gas coefficient (0.14%) so fastest induction and recovery among all agents., more potent (MAC-70%)
  
  • **Advantages** over nitrous oxide is that it has no ozone depleting (greenhouse) effect on environment,
  • no teratogenic effect,
  • no second gas or
  • No diffusion hypoxia and no expansion of air cavities.

• **Disadvantage**
  • very expensive.
  • increase airway resistance in some patients so it should be avoided for asthma patients
Halothane

- Colourless liquid volatile agent
- Pleasant to smell, Non irritant (smooth induction)
- Stored in Amber colour bottles
- (To prevent decomposition by light 0.01% thymol also-added)
- Non inflammable, non explosive
- Max fat gas coefficient (so can get accumulated in obese)
- Can corrode plastic or metals in the presence of moisture
- MAC-0.74%
- Blood gas coefficient - 2.4

Metabolism - 20% is metabolized, main metabolites Trifluoroacetic acid (other bromide, chloride and fluoride in anaerobic conditions)
Effects on other systems

CVS

- ↓ C.O (Bradycardia, direct depression of myocardium)
- ↓ B.P.
- Sensitizes heart to ADRENALINE
other agents which also sensitize are chloroform, cyclopropane, trielene, Methoxyflurane and enflurane

Respiratory system

- Resp. depressant
- max. Bronchodilation in asthmatics

Uterus

- relaxes uterus similar to other agents.
• **Liver** –

• Halothane hepatitis. Incidence of massive hepatic necrosis 1:35,000

• MOA—> more acceptable mechanism is **Immunologic**

• So, guidelines are

  i. Avoid repeated administration at frequent interval (3 months)

  ii. Pre-existing chronic liver disease is not an absolute C/I

  iii. Avoid in patient’s suffering from other autoimmune disease

• -For a known case of halothane hepatitis the inhalational agent of choice is sevoflurane as it does not produce trifluoroacetic acid on metabolism
• ISOFLURANE

• Chemically isomer of enflurane, which is derivative of ether so induction may be irritating
• MAC-1.15
• Blood gas coefficient - 1.38

• Effects:
• CVS: max.↓ PVR (so inhalational agent of choice for producing deliberate hypotension)
• Cardiac output is best maintained so agent of choice for cardiac patients except MI

• Can cause CORONARY STEAL but concern is only theoretical so if necessary isoflurane can be used safely in MI patients

• Resp. - ↓ tidal volume, ↑ frequency

• CNS: ↓CMRO2 (to the extent that it can produce isoelectric EEG) and minimum increase in ICT makes it an agent of choice for neuro surgical anaesthesia
• **Desflurane** — isomer of isoflurane (so irritating induction)

• Lowest B/G coefficient, so best suited for day care surgery

• -Tec-6 special vaporizer is required (because of very high vapor pressure)

  - MAC-6%

• Can produce CO with desiccated soda lime

• Minimum metabolism

• Minimum fluoride

• Preferred for old age, long surgeries, renal and liver patients, obese patients

• **Systemic effects**

  • Isomer of isoflurane so on conc. <6 % (1 MAC) effects are similar to isoflurane but >6% stimulates sympathetic system
• **Sevoflurane**

• Smoothest induction among all inhalational agents

• Agent of choice for pediatric induction. (Induction is rapid also, B/G coff.0.69)

• **Systemic effects**

• Moderate decreases in cardiac output, inhibition of respiration and increase in i.c.t.

• **Disadvantages**

• - High fluoride (in spite no renal failure report because of rapid clearance of fluoride)

• - With soda lime can produce compound A (FGF <21/min, ↑temp)
AGENTS NOT IN COMMON USE
ENFLURANE
- ethereal product
- Can cause epilepsy
- Maximum increase in i.c.t, ↓ in cardiac output and maximum inhibition of respiration
  - produces fluoride (nephrotoxic)
C/I: Epilepsy
  Renal failure

CYCLOPROPANE
Liquid agent
Stored in orange cylinders 75 psi
MAC-9%
BG coefficient - 0.44
Mild irritant
Highly explosive & inflammable
Effects

CVS: Maintains BP (since it stimulates sympathetic system), so it is inhalational agent of choice for shock patients. Can cause cardiac arrhythmias, sensitizes myocardium to Adrenaline

Muscle: Relaxation good
Analgesia – good

Cyclopropane shock — At emergence sympathetic activation goes leading to hypotension

TRIELENE

Colorless liquid, Sweat odor
Mild irritant
Not inflammable
B/G coefficient - 9
MAC-0.2%
With Soda lime produces Dichloroacetylene which is neurotoxic effecting cranial N.; (most commonly 5th & 7th; 3,4,6,10,12 can also be effected & phosgene which is pulmonary toxic (ARDS)

METHOXYFLURANE

Sweet odor
Non irritant
Non inflammable
Most potent inhalational anesthetic
Boiling point>water (105° c)
Highly soluble in rubbers
Good analgesic
Good muscle relaxant
CVS: Sensitizes heart to Adr.

Bradycardia, i C.O.

Liver: Hepatotoxic

Renal - metabolism produces free fluorides & oxalic acid which can cause vasopressin resistant high (Output (polyuric) renal tabular damage.

Chloroform
MAC - 0.8%
BG coefficient - 8.0
No. of cardiac arrests have been reported due to vent. Fibrillation sensitizes myocardium to Adr.
Ether

- Highly inflammable & explosive
- Highly volatile
- Decomposed to light, air and heat (stored in dark bottles)
- Highly irritant vapour, pungent smell (Induction is very unpleasant)
- B/G coef. 12.0 - so induction & recovery are very slow - Cheap
- Can be given by open drop method, requires minimum instruments so can be used at periphery.

Effects

CVS: ↑ sympth. + -> Maintenance of HR & BP  Does not sensitize heart to adrenaline
Resp: ↑ salivation & respiratory secretion, laryngeal spasm may occur

Bronchodilator; so can be safely used in asthmatics
Very high incidence of most of nausea & vomiting
Metabolism does not produce any toxic effect (4% is metabolized)
Anesthetic properties

Best muscle relaxant
V, good Analgesic

Advantages
cheapest
safest
best for remote locations
complete
most near to ideal

Disadvantages
- irritating
- inflammable
- nausea/ vomiting
- larynospam
INTRAVENOUS ANESTHETICS

- Classified as Barbiturate and Non Barbiturates.

BARBITURATES

- Thiopentone sodium - Discovered by Water & Lundy in 1934.
- first i.v anesthetic to be used in clinical practice.
- ultra short acting barbiturates

Physical Properties

- Available as yellow amorphous powder
- H2S like smell
- PH = 10.5 (Highly alkaline a solution)

- Used as 2.5% concentration
- MOA - GABA mediated, at high doses GABA mimetic
Systemic Effects

**CNS:** Unconsciousness is produced in one arm brain circulation time (15 sec.) Consciousness is regained in 10-15 min due to REDISTRIBUTION of drug to viscera, muscle and fat

- Sleep - ↑stage 2, 1 3, 4 and REM
- Anticonvulsant action
- Intracranial tension ↓, Cerebral O2 consumption and metabolic rate of brain so useful for cerebral protection

**CVS:** Causes hypotension due to Venodilation —venous return
Also direct myocardial depressant (at high doses only)

**Respiratory system**
Transient Apnea is very common
Resp. depression at higher doses

**Eyes** ↓intraocular pressure

**Muscles:** - Not a muscle relaxant

**Thyroid** - Antithyroid
Pharmacokinetics

- Elimination half-life - 10.3 hours
- Metabolism - Liver
- 85% is bound to Albumin is plasma

Dose: 5-7 mg/kg

Local Complications

Perivenous and intramuscular injections
Can cause local necrosis of the area that can lead to ulceration

Rx - Prevention —> use 2.5% solution
- Inject very slowly
- Inject in incremental doses

Rx 10 ml of 1% lignocaine with 100 units of hyalase to be injected in that area
Intra-arterial injection –
- best site for iv dorsum of hand
- high alkaline → precipitated in arterial PH → crystal formation → endothelial damage & induces vascular spasm leading to gangrene and necrosis
- Pt. c/o of severe burning pain down the injection site followed by pallor and cyanosis, edema and gangrene.

Prevention
- Don’t use antecubital fossa
- Always use - 2.5%
- Inject slowly and in increments

Rx,
- Leave the needle at site
- Papaverine 40-80 mg in 10- 20ml of saline
- Tolazoline 5 ml or phenoxybenzamine 0.5 mg can also be used
- If none of the above is available 5-10 ml of xylocaine 1%
- Brachial plexus or stellate ganglion block
- Inject 500 units of heparin through this needle (to prevent thrombus)
- Oral anticoagulants for 7-14 days
Contraindications

Absolute –

Porphyria: thiopentone cause LMN paralysis in porphyria patients & even death (can be used
safety in porphyria cutanea tarda)

Relative -

1) Asthmatics
2) heart blocks
3) Hypotension
4) Pat with fixed cardiovascular lesions who can't T C.O. like tight valvular stenosis. Heart
   block, constrictive pericarditis
5) Inflammatory conditions of oral cavity neck where airway maintenance is difficult
6) Dystrophica myotonica (prolonged apnea)
7) Familial periodic paralysis (hypokalemic type)
Methohexitone

2-3 times more potent than thiopentone
Recovery quicker than thiopentone used as 1% solution
Dose = 1 - 1.5 mg/kg
   elimination half life = 4 hrs
It induces seizures so
   anesthetics of choice for ECT
myoclonus can occur
• Non - Barbiturates
• PROPOFOL

• Available as 1% white colour solutions in soya bean oil
• (so injection is painful, 1% xylocaine 2 ml is given along with).
• aquuvavan is a water based preparation approved for use but not widely available

• Contains egg lecithin and no preservative → so high enhance of bacterial contamination
• should be used with in 6 hours
• recently disodium edetete and sodium met bisulphate are antibacterial agents added to propofol

Pharmacokinetics
M0A- through GABA
Onset - 15 sec
Effect - 2-8min
Dose - 2 mg/kg
Metabolism - all products inactive
Effects

RESP:
- Apnea more common & long duration than thiopentone
- Among all iv agents maximum inhibition of airway reflexes is seen with propofol so it is most preferred for laryngeal mask airway (LMA) insertion without use of muscle relaxants.

CVS:
- Hypotension is significant

CNS:
- Cerebroprotective
- Hallucinations, sexual fantasies, opisthoclonus are additional S/E (rare)
• GIT:
  - ANTIEMETIC

• Other:
  • Anti pruritic

• IN ANAESTHETIC OF CHOICE FOR:
  • Day care surgery
  • -recovery rapid and smooth than thiopentone
  • - Metabolic products are active
  • - Short half life
  • - Antiemetic
  • Most preferred agent for laparoscopy (antiemetic)
ETOMIDATE

MOA - through GABA
- Cardiovascular Stable
- minimal resp, depression
- No histamine release

I/v anaesthetic of choice for
- MI patients
- Aneurysm surgery
- Cardiac patients
- Respiratory compromised patients

Side effects - Adrenal suppression
- Highest incidence of Nausea & vomiting (40%)
- Thrombophlebitis
- Painful injection
- Myoclonus

Dose: 0.2-0.3mg/kg
BENZOPYRIPANES
Systemic Effects

CNS
- These are GABA facilitatory
- Mainly acts on RAS (in midbrain) & Amygdale (limbic system)
- Anxiolytic
- Anterograde amnesia
- Not an analgesic
- Anticonvulsant
- Does not ↑ i.c.t.

CVS
Myocardial depression & ↓ B.P. only at high doses mostly cardio stable

Resp.
Resp depression is main cause of death in BZs poisoning

Muscle
Centrally acting Muscle relaxation is seen
Diazepam
- Available as oil base preparation (painful injection)
- t1/2 - 30-60 hrs
- Metabolic products active

Midazolam: unique structure
- water based preparation so injection is not painful
T1/2 - 2-3 hrs. So excellent for day care surgery
- 3 times more potent than diazepam
- Can be given through i/v, i/m, oral, rectal, intranasal so preferred premedicant in children.

Lorazepam: 5 times more potent than Diazepam
- Longest amnesia
- Highest receptor binding potential, so reversal may not be complete with flumenazi
**FLUMAZENIL**

- It is BZD’s antagonist
- given in increments of 0.1-0.2 mg to a max. of 1 mg
- Drawback is that $t_{1/2}$ is 1-2 hrs. so there are high chances of re-sedation
- All actions except amnesia is fully reversed

**Neuroleptanalgesia:**

- Droperidol (2.5mg) + fentanyl (0.05mg): 50: 1 (Available as INNOVAR)

- Useful in surgeries requiring arousable patient like sterotactic brain surgery
- Most common S/E - Hypotension (a blockade), other muscle rigidity', resp.'depression & variable amnesia.

**Neuroleptanaesthesia** - Droperidol + fentanyl + inhalational agent (esp. N20)
KETAMINE
• dissociative anaesthesia
• It can be given by oral, i/m, i/v, intrathecal routes
• Dose - 2 mg/kg i/v
• Metabolized to nor ketamine
• t1/2 - 2-3hrs.

• Effects:
• CNS: - Strong analgesic
  • Dissociative anaesthesia i.e. cortical function & thalamus are inhibited & limbic system gets stimulated producing vivid reactions like Vivid dreaming, Hallucination (40%) & emergence Delirium
  • ↑ the i.c.t so C/I head injuries
  • S enantlomer of ketamine is superior because of lesser side effects and rapid recovery.
  • It is 3 times more potent. It also act on μ receptors
• CVS: ©Sympathetic system so ↑BP
  • ↑pr
• So i/v anesthetic of choice for SHOCK patients

• Resp. - Stimulates respiration at clinically used concentrations
  • -↑ Secretions (larynospasm)
  • - Pharyngeal laryngeal reflexes are preserved so good for full stomach patients (although it does not guarantee 100% protection)
  • - Potent bronchodilator

• Eye - ↑i.o.t.
• Gut: ↑ intragastric pressure, ↑secretion
• Muscle: ↑ muscle tone

Side effects
Commonest is hallucination (40-50%), vivid dreaming (20%), Emergence delirium (10-30%)
Male > Female
Adults > children & old age
To ↓ hallucination (and other effects) agent preferred are benzodiazepines (Opiates & thiopentone are also effective)

↑ muscle tone. pharyngeal, respiratory secretions so premedication with atropine (or glycopyrolate) is necessary

Advantages & uses
1. Can be used as sole anesthetic for minor surgeries/ bum dressings
2. Safest anesthetic to be used as remote places & inexperienced hands (since does not depress respiration)
3. i/v anesthetic of choice for
   - shock patients (maintains BP)
   - Full stomach (preserves pharyngeal & laryngeal reflexes)
   - Asthmatics
   - For induction in CHF, PERICARDITIS, RT-LT shunts
4. alternative method of induction for children (i/m can be given)
OPIOIDS

Opioid receptor → 5 types μ, κ, θ, and nociception

μ₁ - Analgesia, Bradycardia, Miosis, urinary retention and muscle rigidity
μ₂ - Resp. depression, Constipation, Dependence
κ₃ - Mediates supraspinal analgesia
K₁ - Mediates spinal analgesia
σ (Sigma) - Dysphoria
  - Hallucination
  - Tachycardia
  - HT

Nociceptin (Orphanin FQ) {endogenous opioids act through these receptors}
  - Stress response
  - Acupuncture

Resp. depression - Miosis, Dysphoria, Hallucination, Dependence
δ (Delta) - Analgesia (spinal level)
  - Respiratory depression
  - Constipation
CLASSIFICATION

Naturally occurring –
Morphine, Codeine, Thebaine

semi synthetic –
Heroin, Dihydromorphine, Oxymorphone, Pentamorphone

Synthetic-
Butorphenol, Levorphanol, Methadone, Pentazone, Pethidine (meperidine), Fentanyl, Alpentany, Sufentanil, Tramadol

Agonist - Antagonist (mixed opioids)-
Pentazocine, Buprenorphine, Butorphenol, Nalbuphine, Nalorphine, Levallophan, Dezocine, Meptazinol

Pure Agonist morphine Pethidine Fentanyl / Alfentanil / Sufentanil, Remifentanil

Pure Antagonist - Naloxone, Naltrexone, Nalmefene, diprenorphine
• **DRUGS AND RECEPTORS**

- Pure agonists are agonist at all receptors with highest propensity for μ.

- Agonist-antagonist (except buprenorphine and dezocine) are agonist at k & a and antagonist at μ.

- Buprenorphine and dezocine are μ agonist (while action at k, 8 are minimal) at low doses and antagonist at same receptors at high doses.

- Mixed opioids produces ceiling to resp. depression.

- All antagonists are antagonist at all receptors, mainly at μ.
• **Systemic effects of opioids**

• **CVS:**
  - Minimal effects on cvs
  - Hypotension (because of histamine release and decreased sympathetic tone)
  - Shifting of blood from pulmonary to systemic circulation (i.e. why used in Rx of LVF)
  - Bradycardia (except Pethidine, pentazocine & Butorphjenol which causes tachycardia)

• **Respiration:** ↓Resp. (both frequency & tidal volume)
  - ↓Hypoxic & hypercapnic drive

• There may be delayed resp. depression by morphine after epidural route.
  - airway & tracheal reflexes (Sufentanil maximum)
• Bronchi—> Histamine release can cause bronchoconstriction; but direct effect on bronchial muscle is dilatation
CNS
↑I.C.T. in injured brain (so C/I in head injury) and decreases in normal brain

- Stimulates CTZ - Nausea & vomiting (high doses antiemetic)
- Convulsions can occurs (more common with pethidine)

Eye
Miosis (only central action)

Muscle
Muscle rigidity (max.-Alfentanil)
Rigidity in thoracic muscles causes wooden chest syndrome

Renal
- Relaxes UB — Retention

GIT
↓Gut motility, ↓gastric emptying — CONSTIPATION (No tolerance to constipation)
Biliary tract
Causes constriction of sphincter of oddi - ↑ biliary duel pressure

Dependence
Both physical & psychological

Tolerance:
Mainly pharmacodynamic, tolerance is seen with all actions except constipation & miosis

• PETHIDINE (MEPRIDINE)
  • Atropine congener therefore caused atropine like effect like tachycardia, dry mouth or central anticholinergic effect like convulsions ,
  • Action on smooth muscle is less marked therefore can be safely used in biliary colic.
  • Potency 1/10
  • Can cause direct myocardial depression
  • MAO inhibitor can cause fatal reaction due to increased production of nor pethidine
PENTAZOCINE (FORTWIN)
- mainly acts on K receptors at spinal level
- potency 1/3
- ↑Sympath. system causes tachycardia & BP
So C/I in MI patients

BUTOPHANOL: Similar to pentazocine except
1. Less tachycardia
2. More potency (10 times)

BUPRENORPHINE
- 25 times more potent than morphine
- Has highest receptor binding potential

Tramadol
Mainly agonist at (also on δ and K). It decreases serotonin and nor epinephrine reuptake.
Can also cause direct serotonin release
NEWER OPIOIDS

FENTANIL
- 100 times more potent than morphine
  Can be given i.V, ivm, transmucosal, transdeimal, epidural, intrathecal
  - Cardiac stable.

ALFENTANIL
- compared to fentanyl, quick onset and short acting
  - highest incidence of muscle rigidity

SUFEANTANIL
- Most potent (500 times)
  - Opioids of choice for inhibiting cardiovascular response to Laryngoscopy and intubations.
• **REMEFENTANIL**
  - Metabolized by non specific esterase (pseudo cholinesterase)
  - Shortest acting agent of choice for day care surgery
  - Opioid of choice for renal patients
  - Causes significant hypotension
  - Cannot be used for producing analgesia through spinal/epidural because it contains glycine which can cause motor weakness

• **ANTAGONISTS**
• **NALOXONE**
  - Highest propensity to block μ receptors
  - Naloxone also antagonizes the action of
    - Diazepam
    - N20
    - Barbiturates
    - Endogenous opioids
    - Alcohol
• **Other Uses of Naloxone**
  
  a) Neonatal asphyxia  
  
  b) Δ of opioid dependence  
  
  septicemic, Hypovolemic & spinal shock (probably by reversing effect of endogenous-opoids)

• **Dose:** 40-80 jig i/v to a max. of 400 μg  
  
  - Can be given intra-tracheal  
  
  **S/E:** HT, V.fibrillation, pulmonary edema, cardiac arrest  
  
  Short acting (other antagonist naltrexone & nalmefene are long acting)

• **Endogenous opioid**
  
  \[
  \text{Encephalins} \quad \beta \text{ Endorphin} \quad \text{for supra spinal control of pain} \\
  \text{Dynorphins - for spinal control of pain}
  \]

• β endorphins modulates nociception in stress  
  
  Encheptiaiins in acupuncture mediated.
OTHER I.V. AGENTS

PROPAIDID  - obsolete
STEROID AL  - althesin (obsolete)
              - eltanolone
              - GABA

α2 AGONISTS (used as adjuvant)
Properties like sedation, anxiolysis, sympatholysis and analgesia - Clonidine (obsolete)
Dexmedetomidine - newer α2 AGONIST with minimal side effects
MUSCLE RELAXANTS

Physiology of NM Junction

N-M Junction consist of nerve ending, synaptic cleft & muscle and plate
Sequence of muscle blockade

Muscles of larynx, pharynx, face (esp. eye), Jaw —> Resp. & trunk—>limbs—> diaphragm

The sequence at reversal is same.

Importance:

Adductor pollicis is employed for monitoring. The beginning of, blockade in adductor policies ensures that laryngeal, pharyngeal muscles have been blocked & intubation can be performed.

At reversal return of power in adductor ensures return of power in laryngeal, pharyngeal and respiratory muscles.
**Depolarizing relaxants**
- Dexamethonium - not used
- Suxamethonium (Succinyl choline)

**SUXAMETHONIUM**
Discovered by Bovet
Onset of action - 20-30 sec
Duration of action - 3-5 min.
ideal for difficult airway management situations.

**Metabolism:** metabolized by plasma- pseudo-cholinesterase which is synthesized by liver and present in plasma
Mech. of action of Depolarizing agents

Drugs act like Acetylcholine attaching to Ach receptors causing depolarization & action potential—muscle fasciculations.

Sustained stimulation will make the membrane to become refractory causing neuromuscular blockade.

ACTIONS

1. CVS: Bradycardia due to muscarinic effect ↑s chances of ventricular arrhythmias (↑ K+)
**HYPERKALEMIA:**

- Due to excessive muscular fasciculations
- ↑ Intraocular pressure
- Intragastric pressure
- Muscle pains in post operation period.
- Can be decreased by
  - a. Precurarization with non-depolarizing agents
  - b. Self taming (giving in 2 divided doses)
- Masseter spasm - seen in children
- GIT - ↑ salivation
- ↑ Gastric secretion
- Anaphylaxis
- Malignant hyperpyrexia – most commonly implicated Drug
Contra indications

1. Hyperkalemia
2. Newborn (Avoid in children)
3. Head injury \[ Upto 2-3 months after trauma \]
4. Glaucoma, penetrating eye injuries
5. Upto 2-3 months after trauma
   Upto 6 months after hemiplegia / paraplegia (max. risk period is 1-8 weeks)
   Hyperkalemia
   Upto 1 year after burns.
Extrajunctional receptor: seen in neonates infants deinnervated or injured muscle. These are very sensitive to depolarizing agents (but resistant to NDMR)

6. Renal failure (if Hyperkalemia is existing)
7. advanced liver failure
8. Mwml
9. shock
10. Diagnosed case of low pseudo cholinesterase level
11. Atypical pseudo cholinesterase (incidence 1:3000)
12. Duchene muscle dystrophy
13. Dystrophia myotonica
• PROLONGED BLOCK AFTER Sch

• Low Pseudo-cholinesterase levels
• Liver diseases
• Pregnancy, Uremia, hypoproteinemias, new borns, alcoholics, nephrosis, Cancer - cytotoxic drugs (Alkylating agents)
• Organophosphates
• -Neostigmine & Pyridostigmine
• -Pancuronium, metoclopramide

• Treatment.
• IPPV\FFP\synthetic cholinesterase

• 2. Atypical pseudo cholinesterase
• Genetic disease,
• diagnosed by dibucaine no
Dibucaine no. –

• Dibucaine inhibits 80% of normal pseudo cholinesterase & 20% abnormal enzyme.

• Dibucaine number only indicates the genetic makeup of individual. It can not measure the concentration or efficiency of pseudo cholinesterase.

• Na fluoride can be used in place of Dibucaine (fluoride number):

• Trt same as of low pseudo cholinesterase
3. Phase II block (dual block): This is a prolonged block seen after over dosage of sch (>5 mg/kg) or >500 mg.

Fading on train of four is diagnostic
Reasons may be

b) Desensitisation of receptor
c) Channel blockade
d) Ca2+ mediated iniurv to end plate

**TREATMENT**

- Continue IPPV
- spontaneous recovery
- neostigmine
### NON-DEPOLARIZING AGENTS

<table>
<thead>
<tr>
<th>Steroidal compounds (vagolytic)</th>
<th>Benzylisoquinolinium compounds (release histamine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>-d tubocurare</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>-metocurine</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>-Doxacurium</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>-Atracium</td>
</tr>
<tr>
<td></td>
<td>-Cis- atracurium</td>
</tr>
<tr>
<td></td>
<td>-mivacurium</td>
</tr>
</tbody>
</table>

Others—Gallamine Accuronium

### AGENTS NO MORE USED

- D. Tubocurare (named because it was transported in bamboo tube & used as arrow poison by Amazon people)
- Maximum propensity for releasing Histamine
- Maximum propensity for ganglion blockade can cause severe Hypotension
**Gallamine**
- Only non depolarizer to cross placenta
  - Max. Propensity for vagal blockade, so cause tachycardia
  - Excreted unchanged (80%)

C/I — Renal failure
  Pregnancy

**Alcuronium**
- Anaphylaxis very common
- Deterioration on exposure to sunlight

**Metocurine** - Semi synthetic derivative of dT with less cardiovascular effects
• **AGENTS USED NOW A DAYS**

• **DOXACURIUM**: most potent, almost not metabolized
• excreted unchanged through kidneys
• longest duration (60 min.) muscle relaxant therefor not preferred.

• **PANCURONIUM**
• -Steroid compound
• Duration of effect - 30-40min.
• Not used commonly because of cardiac instability (release Nor Adrenaline so tachycardia & ↑BP and ↑Chances of arrhythmias with halothane)

• -Relaxant of choice in arterial surgeries where BP maintenance is required or hypotensive patients.
• **VECURONIUM**
  
  • Effects: most CVS stable
  • Duration 15-20min.
  • Metabolism: 30-40% metabolized in liver & rest excreted unchanged Significant amount excreted in bile (40%)
  • can cause polyneuropathy on prolonged use in ICU

• **ATRACURIUM**
  
  • Available as Atracurium Besylate
  • Duration 15-2Umm.
  • Metabolism: metabolized by Hoffman degradation (95%) in plasma & ester hydrolysis (5%)
It is relaxant of choice in

1. conditions where reversal is contraindicated
2. Renal failure
3. Hepatic failure
4. Neuromuscular diseases
5. Neonates

- Metabolism produces Laudanosine, which crosses Blood Brain Barrier & can produce Convulsions.

- Releases histamine causing allergic reactions ranging from pruritic rash to angioneurotic edema can occur
• **NEWER NDMR:**

• **Pipecuronium** - It is pancuronium derivative.
  - No vagolytic or ganglion blockade action so cardiovascular stable.

• **Rocuronium**
  - 8 times less potent than vacuronium.
  - Onset of action 60 sec. (other nondep 3-4 min),
  - so it is non depolarizes of choice for intubations and precrurarization

- Rest pharmacology is similar to vacuronium.
- (But not as cardiac stable as vecuronium)

- **Rapacuronium**:
  - half duration than Rocuronium but withdrawn from the market because it produced intense bronco spasm in very significant no. of patients (> 9%)
- **Cis-astracurium:**
  - stereoisomer of Atracurium,
  - 4 times more potent,
  - no histamine release,
  - 5 times less laudonosine production and is metabolized in similar way like atracurium

- **Mivacurium:**
  - Benzyliisoqumolinium
  - metabolized by pseudo cholinesterase
  - Duration of action: 5-10 min.
  - therefore muscle relaxant of choice for day care surgery.

- S/E: histamine release
• **Mixed onium chlorofumrate (430A)**

• **Gantacurium** previously known as AV430A
  • still in phase HI clinical trials.
  • Preclinical trials has proved it to be having fast onset (< 90 seconds) and ultra short acting (shortest among non depolarizers),
  • after reversal complete recovery has been reported in 3-4 min

• It is rapidly metabolized by forming cysteine adduct followed by ester hydrolysis

• gantacurium will not be the only non depolarizer of choice for intubation rather it may emerge as an alternative to suxamethonium for intubation
NDMR do not cross Blood Brain Barrier & placenta in significant amounts so can be given safely.

**FACTORS FROlONGING THE N-M BLOCKADE**

1. Elderly patients
2. Paediatric patients
3. Obese (steroidal)
4. Renal disease (except Atracurium)
5. Hepatic disease (except Atracurium)
6. Centrally acting (Inhaled anesthetics, benzodiazepines) or peripheral acting (Dantrolene, mephensin) muscle relaxants
7. Hypothermia
8. Antibiotics (amino glycosides and Tetracycline)

9. Local anesthetics (stabilizes post synaptic& muscle except Procaine which can reverse the block membrane)

10. Ga2+ channel blockers, Hypolcalcemia

11. Hypokalemia

13. Magnesium

14. Lithium

15. Neuromuscular diseases
Drugs which can shorten the block
- Procaine
- Phenytoin
- Carbamazepine
- Calcium
- azathioprine
- steroids
REVERSAL OF BLOCK

- give reversal with NDMR (avoid only if absolutely C/I)
- give reversal only when some spontaneous activity in muscles begins

Drugs used for reversal are

- Neostigmine
- Endrophonium
- Pyridostigmine

Atropine or Glycopyrolate (to prevent muscarinic effects like Bradycardia, intestinal peristalsis, Bronchospasm, salivary secretions, miosis, contraction of bladder which are because of increased Ach)

**MOA:** Inhibition of Acetyl cholinesterase ↑Ach levels at N-M Junction
Neostigmine

- Quaternary ammonium compound so does not cross BBB
  Dose - 0.04 to 0.08 mg/kg along with atropine 0.02 mg/kg or glycopyrolate (0.01 mg/kg)
  Duration - 2 hrs. Peak effect - 10 min.

Short duration so chances of recurarization are high

Endrophonium does not inhibit pseudocholinesterase therefore reversal agent of choice for mivacurium

Pyridostigmine: Duration of action is longer (6hrs.) so useful in renal failure patients

Gamma Cyclodextrins are the reversal agents which directly bind to steroidal type of muscle relaxants, Not useful for benzyisoquinolones.
• **SIGNS of Adequate reversal**

  - Regular respiration with adequate tidal volume
  - Spontaneous eye opening
  - Spontaneous limb movement
  - Able to protrude tongue
  - Able to cough
  - No cyanosis
  - Able to lift head > 5 sec
  - Able to hold tongue depressor between central incisors

  • Most reliable clinical test to assess recovery from the effect of muscle relaxants followed by head lift > 5 sec

  • Train of four ratio more than 0.9 – guaranteed recovery
## Classification of Peripheral N.

<table>
<thead>
<tr>
<th>Fiber class</th>
<th>Sub class</th>
<th>Myelin</th>
<th>Diameter</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>α</td>
<td>+</td>
<td>6-22 μ</td>
<td>Motor, proprioception</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>+</td>
<td>6-22 μ</td>
<td>Motor, proprioception</td>
</tr>
<tr>
<td></td>
<td>γ</td>
<td>+</td>
<td>3-6 μ</td>
<td>Muscle tone</td>
</tr>
<tr>
<td></td>
<td>δ</td>
<td>+</td>
<td>1-4 μ</td>
<td>Pain, touch, temp.</td>
</tr>
<tr>
<td>B</td>
<td>i</td>
<td>+</td>
<td>&lt; 3 μ</td>
<td>Autonomic functions (preganglionic sympathetic)</td>
</tr>
<tr>
<td>C</td>
<td>SC</td>
<td></td>
<td>0.3-1.30μ</td>
<td>Autonomic functions (postganglionic sympathetic)</td>
</tr>
<tr>
<td></td>
<td>DyC</td>
<td></td>
<td>0.4-1.2 μ</td>
<td>Pain, temperature touch</td>
</tr>
</tbody>
</table>
• Small diameter axons like c fibers are more susceptible to local anesthetic block than large diameter fibers like Aa but myelinated are more readily blocked / sequence is B → C → A (Even there are enough studies to prove that due to more number of nodes of ranier A delta and A gamma fibres are blocked earlier than B fibers)

• → Sequence of blockade Automatic → sensory → motor
• → Sequence of recovery motor → sensory → automatic
• → In somatic (sensory) blockade order is temp (cold < hot)
  → pain → touch → deep pressure
• → proprioception
• Classification of local anaesthetics

• Aminoamides
  - Lidocaine
  - Mepivacaine
  - Prilocaine
  - Bupivacaine
  - Etidocaine
  - Ropivacaine

• Aminoesters
  - Procaine
  - Chlorprocaine
  - Tetracaine (amethocaine)
  - Benzocaine
  - Cocaine
<table>
<thead>
<tr>
<th>Esters</th>
<th>Amides</th>
</tr>
</thead>
<tbody>
<tr>
<td>-hydrolyzed in plasma by cholinesterase (except cocaine)</td>
<td>-hydrolyzed in liver</td>
</tr>
<tr>
<td>-unstable</td>
<td>-stable solutions (can be autoclaved)</td>
</tr>
<tr>
<td>-high incidence of Allergic reactions (because of p.aminobenzonic Acid)</td>
<td>-low incidence</td>
</tr>
</tbody>
</table>
Short duration: Low potency
- Procaine
- Chlorprocaine - Shortest acting

Intermediate duration: Intermediate potency
- Lidocaine
- Mepivacaine
- Prilocaine
- Cocaine

Long duration; High potency
- Bupivacaine
- Tetracaine
- Etidocaine
- Ropivacaine
- Dibucaine - Longest acting
• **MECHANISM OF ACTION**

• un-dissociated form penetrates the axonal membrane
• gets dissociated
• binds to receptor situated in Na⁺ channel from inner side
• blocking the channel.

• Not only on Na⁺ channels but also act on K⁺ & Ca^2+ channels
• can block both activated & non activated channels but activated channel are more readily blocked.
• LA themselves can activate inactivated channel.

• **Metabolism**

• Esters undergo hydrolysis by plasma pseudo cholinesterase while amides undergo hydrolysis or dealkylation in liver
• **General considerations in action of Local anesthetics**

• Absorption Systemic absorption depends on
  - site of injection
• The systemic absorption of LA after nerve blocks is as follows: intercostals > caudal > Para cervical > epidural > brachial plexus > sciatic
  - dosage
  - addition of vasoconstriction

• **Anesthetic potency** - Depends on lipid solubility

• **Duration**
  - Type of the drug used (most important factor)
  - Dose
  - Addition of vasoconstrictors; Adrenaline 1 in 2,00,000 (5mic/ml)
  - Addition of soda bicarbonate (on metabolism produces CO2 which changes inside pH to acidic)
**Onset of action** - Depends on
- Dose
- Concentration
- PKa (Drug with lower pKa {7.7} lidocaine are fast acting, with high pKa 8.4.
Bupivacaine are slow acting)
- Type of nerve fiber
- Adding sodabicarb. (Making more drugs to be available in non ionized form)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency</th>
<th>11/2</th>
<th>duration (with Adr)</th>
<th>Without Adr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine =</td>
<td>1</td>
<td>30-90 min</td>
<td>15-30 min</td>
<td></td>
</tr>
<tr>
<td>Chlorprocaine</td>
<td>1</td>
<td>30-90 min</td>
<td>15-30 min</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>2</td>
<td>-</td>
<td>2-3 hrs</td>
<td>-</td>
</tr>
<tr>
<td>→Lignocaine</td>
<td>2</td>
<td>1.6 hrs</td>
<td>2-3 hrs</td>
<td>30-60 min</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>2</td>
<td>1.5 hrs</td>
<td>2-3 hrs</td>
<td>30-60 min</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>2</td>
<td>1.9 hrs</td>
<td>2-3 hrs</td>
<td>30-60 min</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>6</td>
<td>2.6 hrs</td>
<td>3-5 hrs</td>
<td>2-3 hrs</td>
</tr>
<tr>
<td>→Bupivacaine</td>
<td>8</td>
<td>3.5 hrs</td>
<td>3-5 hrs</td>
<td>2-3 hrs</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>8</td>
<td>3-5 hrs</td>
<td>2-3 hrs</td>
<td></td>
</tr>
</tbody>
</table>
**TOXICITY OF LA:** CNS & CVS toxicity get increased in shock (diversion of blood)

**CNS**
- Initial symptoms are light-headedness, dizziness, circum oral numbness, visual & auditory disturbances, disorientation. Muscle twitching, tremors & convulsions followed by CNS depression.

**CVS**
- All have negative inotropic action but Bupivacaine can cause ventricular tachyarrhythmia.
- At doses used in clinical practice-vasodilators
- except cocaine and S isomers i.e. levo bupivacaine and ropivacaine which are vasoconstrictors
Methemoglobinemia - seen with large doses of Prilocaine, benzocaine, lignocaine.

**Allergic reactions:** more common with esters.

**Local toxicity:** If directly injected in the nerve.

Most neurotoxic - chlorprocaine.

Lignocaine and tetracaine can cause cauda equina syndrome.

LA with ADRENALINE cause gangrene if used in Nerve blocks Ring Block -
- fingers
- toes
- penis
- pinna
**COCAINE**

- Effects: CNS - stimulation
- Eye-Mydriasis
- Used as 4% strength for surface analgesia
- not metabolized by pseudo cholinesterase
- potent vasoconstrictor (Not to be given i/v)

**PROCAINE**

- 1-2% cone, is used for nerve blocks
- metabolized by pseudo cholinesterase
- LA of choice in pat. with history of malignant hyperthermia

**CHLORPROCAINE**

- shortest acting
- Not to be used for spinal (can cause neurological deficits)

**PRILOCAINE**

- Safest LA
- Pharmacologically similar to Lignocaine except extra Hepatic Sites -
- Kidneys, lungs →by amidase

- & high propensity to produce methaemoglobinaemia (usually in high doses only)
- O-toluidine is metabolic product of prilocaine which is responsible for methhemooglobinemia
• **LIGNOCAINE (Lidocaine, xylocaine)** –
  • most commonly used LA
  • pKa-7.8
  • Concentration used
  • 4%-Surface (topical) analgesia
  • 1 %-Nerve blocks 0.5%-intravenous
  • 1-2%-Extradural regional anesthesia (Beirs blocks)
  • 5%-Spinal
  • 2%Jelly for urethral procedures

• Dose: max. Safe dose - 4.5mg/kg or 300 mg without Adrenaline.
  • 7mg/kg or 500 mg with Adrenaline
• Other uses: Used for ventricular arrhythmias (As xylocard 2% 2mg/kg)

• Blunting response to intubation

• -not to be used in patient with H/O malignant hyperthermia (it releases Ca2+ from sarcoplasmic retinaculum)
• **BUPIVACAINE:**
  - Long acting LA
  - PK-8.2
  - 8 times more potent than xylocaine

• **Concentration used**
  - 0.5% for nerve blocks
  - 0.5% Spinal
  - 0.125-0.25% painless labor and postoperative analgesia—most preferred for this purpose because it has wide DIFFERENTIAL SENSORY\MOTOR BLOCKADE

• **Max. Safe dose** - Without adrenaline: 2.5 mg/kg
  - With adrenaline: 3 mg/kg
• Cardio-toxic potential is much higher than Xylocaine so not used in intravenous regional analgesia

• Cardiotoxicity ↑es in PREGNANCY, hypoxia & percarbia
• D.O.C for ventricular arrhythmia by Bupivacaine is bretylium
Levo bupivacaine is S isomer of bupivacaine. Less cardio toxicity and neurotoxicity than bupivacaine.

Although its cardiotoxicity is lesser than bupivacaine but still high enough to contraindicate its use for intravenous regional anesthesia.

Maximum safe dose of levobupivacaine are similar to bupivacaine i.e. 2.5 mg/kg (maximum 175 mg)

It is 13% less potent than bupivacaine therefore duration (which is directly proportional to potency) and quality of block of block will be proportionately less. (but clinically this difference is almost negligible)
ROPIVACAINE

To further reduce the cardiotoxicity of levo bupivacaine its butyl groups were replaced by propyl group producing the drug called as Ropivacaine

Maximum safe dose - 3mg/kg (maximum 225 mg)

cardiac arrest following ropivacaine has much better prognosis.

Another advantage of ropivacaine is that its cardio toxic potential is same in pregnant versus non pregnant females (while toxicity of bupivacaine is considerably higher in pregnancy).

Ropivacaine is slightly lesser potent than levo bupivacaine so slightly less motor block, and slightly less duration

Another difference which occurred due to these chemical change is that levobupivacaine and ropivacaine became vasoconstrictor while bupivacaine is vasodilator
DIBUCAINE
Longest acting, most potent and most toxic

LA FOR TOPICAL:
Can’t be used- Bupivacaine ropivacaine and mepivacaine (procaine and chlorprocaaine-> poor penetration)

EMLA (eutectic mixture of local anesthetics)
CREAM 5% lignocaine+5%prilocaine Onset slow (1 hr)
PRINCIPLES OF REGIONAL ANESTHESIA.
• CENTRAL NEURAXIAL BLOCKS
• SPINAL / EPIDURAL

• APPLIED ANATOMY
• Spinal cord occupies the whole vertebral column in intrauterine life
  • in infants ends at lower border of L3
  • in adults it extends up to lower border of L1. (Achieved by 2 years).

  • Dura extends up to S2 and Pia (as filum terminale) up to coccyx

  • Layers: It is covered by 3 layers from outside inside; dura → arachnoid → pia

  • CSF is present in subarachnoid space

  • Extradural veins (plexus of batsons) - valve less veins extending from cranium (intracranial sinuses) to pelvis and are in direct communication with IVC
• Structural encountered during spinal anesthesia
  • skin
  • subcutaneous tissue
  • Supraspinous ligament
  • Interspinous ligament
  • Ligament flavum
  • Dura
  • Arachnoid

• Imp. Surface landmarks
  • C7 is very prominent & easily palpable
  • T7 lies opposite to inferior angle of scapula
  • Highest point on iliac crest corresponds to L4-5 interspace
  • Nipples corresponds to T4
  • Xiphistemum to T6
  • Umbilicus to T10
  • Inguinal ligament to L1
SPINAL ANAESTHESIA SUBARACHNOID BLOCK
INTRATHECAL BLOCK

INDICATIONS

Excellent for

- Orthopedic surgery of lower limbs & pelvis
- Gynaecology & obstetrical surgeries
- Hernias, hydrocele, Appendix & other lower abdominal surgeries
- Perineal surgeries

It can be performed in

- Lateral position
- Sitting position
- Prone position

Approach may be midline or paramedian
• **Needles**

  - Dura cutting (Quincke-Babcock) - more post spinal headache
    
  - Dura separating (pencil tip point end like Whitcre type, Sporte) - less post spinal headache

• **Drugs**

  1. Xylocaine (Lignocaine) 5% Heavy i.e. Hyperbaric i.e. SG > CSF (1004)
     - It is made heavy by addition of dextrose 7.5%

  2. Tetracaine 0.5% in 5% dextrose (not used in India)

  3. Bupivacaine 0.5% in 8% dextrose
Factors effecting height of block very significantly

- Volume (dosage) of drug.
- Baricity
- Position of patient
- Site (inter vertebral space) of injection

- Intra-abdominal pressure; ↑ed ascites, abdominal tumours pregnancy - dose to be reduced by 30-40%

- CSF volume: inverse relation with the level of block
B. **Factors which effect the level of block but not very significantly**

1. Age - old age

2. Obesity: Morbid obesity only

3. Height: inverse relation with the level of block

4. Spinal curvature: severe Kyphosis may lead to higher spread of drug.

5. Direction of needle:
C. **Factors not effecting the level of block**

1. Sex

2. Speed of injection

3. Increased CSF pressure seen during Barbotage (It is the technique in which repeatedly CSF is taken out and drug is injected), coughing or straining does not effect the level of block.

4. Addition of vasoconstrictor.
Systemic effects of spinal anaesthesia

CVS
-Sympathetic block cause HYPOTENSION which is because of ↓venous return

So causes of hypotension are:

1. ↓Venous return (because of dilation of veins)
2. Bradycardia-↓C.O.
3. Blockage of adrenal glands: Supply of catecholamines
4. Direct absorption of drug in systemic circulation
II CNS

Autonomic level is 2 segments higher than sensory which are 2 segments
Higher than motor

III Resp. - dyspnoea, apnoea

Causes of Apnea are

1. Hypotension severe enough to cause medullaiy ischemia
2. High spinal (to block even phrenic C345)
3. Total Spinal
4. Intravascular injection

Rx- IPPV or intubation
- Treat hypotension
• IV G.I.T.

• Sympathetic block → increased peristalsis
• Relaxed sphincters
• Reasons for nausea & vomiting

• a) Hypotension central hypoxia N&V
• b) Abdominal structure handling
• c) Due to bile in stomach (feiaxed pyloric sphincter)
• d) Psychological
V. **Stress response:** blocked by spinal

VI. **Temp.**: vasodilatation causes heat loss shivering (Shivering increased O2 requirement by 4 times)

Drug of choice for treatment of shivering is pethidine followed by Tramadol.

VII. **G. U. system:** urinary retention
Flaccid and engorged penis
Complications of Spinal Anaesthesia

During surgery

1. Hypotension - most common complication
   Rx prophylactic preloading with 1-1.5L of fluids
   Curative:

   1) Head low position (Trendenlenburg) [15° - 20°]
   2) Infusion of fluids
   3) Vasopressors - ephedrine 2-6 mg
      - mephenteramine
      - Dopamine (no direct role)

2. Bradycardia

   Reasons: parasympathetic over-dominance, inhibition of cardio accelerator fibres Rx - Atropine
3. **High Spinal**

   Complications depends on level if upto block cardioaccelator fibers then Bradycardia & hypotension if involves cervical—>
   Diaphragmatic paralysis occur

   RxIPPV

4. Resp. paralysis (Apnea)

5. Nausea & vomiting

   Rx - oxygenation
   Correct hypotension
   Antiemetic

6. Apprehension & anxiety

   Rx-sedate the patient
1. Urinary retention - now a days most common post op. complication

2. Neurological complications:
   
a. **Post spinal headache**
   - low-pressure headache due to leakage of CSF
   - Usually occipital (but can be in any region), with neck pain & stiffness (postural relation)
   - Present after 12-24 hours.

   90% relieved in 7-10 days and in almost all cases in 3 weeks
**Rx-Preventive**

1. Use of small gauge needles
2. Use of pencil tip (dural separating) needles
3. Adequate hydration
4. Early ambulation does not increase the incidence of post spinal headache

1\textsuperscript{st} line  Analgesics, hydration i.v/oral, position- supine

2\textsuperscript{nd} line  Caffeine, 5% carbon dioxide desmopressin

3\textsuperscript{rd} line  - Injection of 15-20ml of autologous blood in epidural space
b. Other rare complications

- Cauda equina syndrome (more common with continuous spinal)
- Paraplegia (mostly because of epidural hematoma)
  - Rx: drainage of hematoma
- Paralysis of cranial N. (6th MC) (1, 9th, 10th are not involved)
- Anterior spinal artery syndrome & cord ischemia (if vasoconstrictor used),
- Adhesive arachnoiditis - inflammation of arachnoid due to reaction by preservatives
  - Use preservative free LA
- Meningitis
- Intracranial complications - bleeding or herniation due to sudden changes in pressure
  - 3. Backache
EPIDURAL ANAESTHESIA/EXTRADURAL BLOCK/PERIDURAL BLOCK

- The drug is injected outside the dura
- Usually used for post-op. analgesia and painless labor.

Methods-
Needle used in Tuohy needle
  Epidural space has negative pressure (in 80% individuals)
  → Hanging drop technique (Gutierrez’s sign) sudden sucking of drop in epidural space- rarely used
  → Loss of resistance technique- most commonly used

Drugs:
Lignocaine 1-2% 2-3 ml of drug is required to block 1 segment
Bupivacaine 0.125%-0.5%
Advantages over spinal

1. Less hypotension
2. No post-spinal headache
3. Level of block can be changed
4. Any duration of surgery can be performed
Disadvantages

1. Patchy block very common (L5S1-usually spared)

2. Chances of unsuccessful block high

3. Epidural hematoma can cause paraplegia

4. High chances of total spinal (because of accidental dural puncture)
   So inject in increments of 3-5 ml only after negative aspiration of CSF

5. Intravascular injection of drug is more common

6. Technically difficult

7. Expensive

8. Effect takes place in 15-20 min.
**Caudal block**

- Drug injected (xylocaine 2 mg/kg) in sacral hiatus
- Most commonly used in children
- Good for perineal surgeries

**Saddle block**

Kind of spinal block given in sitting position and patient remains seated till drug gets fixed to sacral segments only, so useful for perineal surgeries
C/I OF CENTRAL NEURAXIAL BLOCKS

Absolute
1. Raised i.c.t.
2. Bleeding diatheses
3. Patients on anti-coagulants —....
4. Severe hypovolemia
5. Infection at local site
6. Refusal of patient
7. Severe aortic and mitral stenosis
• Relative
  • mild to moderate hypotension, hypovolemia
  • HT (uncontrolled)
• Severe ischemic heart disease especially history of recent MI.
• Thrombocytopenia:
  • Heart blocks & patient on beta blockers: Severe bradycardia can occur.
• Spinal deformity: Technically difficult.
• Previous spinal surgery.
• Psychiatric disorders.
• History of headaches.
• Uncooperative patient.
• GIT perforation: Parasympathetic over activity increases peristalsis and can open the seal.
• Neuropathies: Important from medicolegal point.
• CNS disorders: Both infective and degenerative.
• Resistant surgeon
• Chronic backache
• Septicemia and bacteremia
Opoids for central neuraxial blocks

Advantage over LA:

1. No motor block
2. No sympathetic block

Disadvantage: respiratory depression (delayed with morphine)

For intrathecal: very high chances of resp. depression if higher doses are used

For epidural
Morphine 4-6 mg (diluted in 10 ml saline), onset 30 min, last for 12-16hrs.

100μg of fentanyl (diluted in 10 ml saline) onset 10 rain, last for 2-3 hrs.
Level of block required for common surgeries

- LSCS-up to T6
- Prostate-up to T10
- Kidneys-up to T6
- Testicular surgeries-up to T10
  - Perineal-Sacral plexus block is sufficient
- Hemia-up to T10
- Appendix-Tg-T10
PERIPHERAL NERVE BLOCKS

BRACHIAL PLEXUS BLOCK

Can be blocked by:

1. **Interscalene approach**: Brachial plexus is blocked between anterior and middle scalene. Chances of sparing of ulnar nerve are high

Complications:

1. Phrenic Nerve block
2. Epidural & intrathecal injection
3. Horner syndrome
4. Other like neuritis, Intravascular injection or injury to nearby structures
2. Supraclavicular block:
- Most commonly used approach
- blocked lateral to subclavian artery (to prevent pneumothorax)

Complications:
1. Pneumothorax (0.5-6%)-98% resolve by themselves
2. Phrenic N. block (40-60%)
3. Homer syndrome (due to block of cervical symp. Chain)
   - Ptosis
   - Miosis
   - Absence of papillary dilatation on shading the eye
   - Enophthalmos
   - Anhydrosis over the ipsilateral face & neck
   - Absence of ciliospinal reflex (Dilatation of pupil when skin over neck is pinched)
4. Other like neuritis, Intravascular injection or injury to nearby structures
**Axillary Approach:** Very commonly used block

**Adv.:** No chances of pneumothorax & phrenic N. paralysis

**Disadv:** Musculocutaneous N. & intercos to branchial (T2) are spared; so difficult to use in arm surgery

**Complications:**

- Intravascular injection
- Hematoma
- Infection
- Neural injury
**Infraclavicular approach**

Brachial plexus is blocked either just below the mid point of clavicle (classical approach) or just medial to coracoid process (coracoid approach). The theoretical advantage is that musculocutaneous and axillary nerve can be blocked.

Due to high failure rate and increased incidence of pneumothorax and haemothorax (in classical approach) **this block is not practiced routinely.**

- Each nerve can be separately blocked separately at elbow or wrist
Intravenous Regional Blocks (Bier’s block)

First described by August Bier

Adv.
- Easy procedure
- Success rate is almost 100%
- Rapid onset
- Good muscle relaxation

Complications
1. Accidental deflation or leak can cause drug toxicity & death
2. Tourniquet related problems like discomfort, difficulty in providing blood less field or

Compartment syndrome
- Bupivacaine is not recommended for this technique
Lignocaine 0.5% (5mg/kg) or Prilocaine can be used (and now a days ropivacaine also)
LOWER EXTREMITY BLOCKS

3 in 1 block (perivascular block) Drug is injected in femoral canal while maintaining distal pressure vill result in spread of drug resulting in lumbar plexus block.

- femoral N. block
- obturator N. block
- sciatic N. block
- Ankle block (Deep peroneal, Superficial peritoneal & saphenous N. are blocked)
BLOCKS OF HEAD & NECK

- Trigeminal N. block
- Gasser Ian ganglion block - for Trigeminal neuralgia
- Cervical plexus block - for carotid endarterectomy

**Stellate ganglion block:** It is blocked anterior to the tubercle of transverse process of C6 (chassaignac tubercle)
Used for upper extremity sympathetic dystrophies

Signs of successful block

- Homer syndrome
- Conjunctival congestion - usually earliest sign
- Nasal stuffiness (Guttmann’s sign)
- Tympanic membrane congestion (Muller sign)
- Vasodilatation
- Skin temp.
Complications

- Brachial plexus block
- Recurrent laryngeal N. block
- Phrenic nerve block
- Haematoma formation
- Epidural & intrathecal injection
- Intravascular injection
- Bradycardia, hypotension

Phrenic N. block posterior border of SCM 3 cm superior to clavicle
Airway block (used for awake intubation/broncoscopy)
Usually done under topical analgesia with fibreoptic bronchoscope
Otherwise

1) Glossopharangeal- base of anterior tonsillar pillar
2) superior laryngeal- &elow tip of greater cornu of hyoid bone
3) recurrent laryngeal- transtracheal (cricothyroid membrane)
Block of abdomen & thorax

- intercostal N. block (Ghast tube, post herpetic neuralgias, rib fracture) - maximum systemic absorption

- celiac plexus block (most common complication- Hypotension)

- Lumbar sympathetic chain block for Burger disease (RSD for lower limb)