***Summary; Pharmacology of the Anesthetics***

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***Reference: Lecture & Notes***

***Anesthesia*** characterized by; Hypnosis + Paralysis + Analgesia

***Types of anesthesia***: General “IV and Inhalational” & Local “Injection and Block”

***Area of action***: **Cortex**, **Hippocampus**, Thalamus, Brain stem, Nerves and **Spinal cord**.

***MOA***: Chloride channel GABAA-Agonist – NMDA-Antagonist – Neuronal Nicotinic-receptor –

Glycine gated chloride channel

***Mean alveolar concentration “MAC”***: The minimum % of anesthetic agent in the alveoli that leads to sedation in 50% of subjects.

Not exceed 1.5 MAC – 2-3 MAC is lethal – 0.4 MAC patient is going to awake.

***Partial pressure “PP” of the brain***: The % of anesthetic agent in brain tissue.

***Guedel’s stages of anesthesia***: Higher to lower suppression as medulla depress last.

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| **1st Induction** | **2nd Excitement** | **3rd Surgical anesthesia** | **4th Medullary paralysis** |
| **-Consciousness to unconsciousness**  -Reflexes & respiration normal  -Hear, see, dream  -**Can do minor operation** such MRI, Colonoscopy not major procedure | -Delirium  -Irregular BP & RR  -Laryngospasm “Possible”  -Dilated pupil  -**NO procedure** | -Regular respiration to cessation of spontaneous breathing.  -Phases:  1st Roving pupil  2nd Loss of corneal & laryngeal reflexes  3rd Dilated pupil & light reflex lost.  4th Dilated pupil,  shallow abdominal respiration & intercostal paralysis.  -Reduce muscle tone, respiration, BP but increase HR with weak pulse.  -**Procedure is done.** | -Cessation of breathing  -Failure of circulation  -Dilated pupil  -Flabby muscle  -Thready pulse  -Low BP  -Death |

***Phases of anesthesia***: Induction > Maintenance > Recovery

***Factors affecting PP of anesthetic***: **1-** PP of anesthetic in inspired gas

**2-** Ventilation “Delivery to alveoli”

**3-** Alveolar exchange “V/P”

***Ideal anesthetics***: For patient / For surgeon / For anesthetist

***IV anesthetics***:

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| Agent | Uses | Advantages | Disadvantages |
| Benzodiazepines ”BZ”;  Midazolam “Most potent & water soluble & short acting”  Diazepam  Lorazepam | Pre-op anxiolytics.  Sedation “NOT ALONE” | Rapid onset  Amnesia  Anticonvulsant  Minimal CV effect | Long acting “Diazepam/ repeated inj. Of Midazolam”  Not analgesic  Respiratory depression |
| Barbiturates;  Not for asthmatics  Thiopental, Thiamalyl  & Methohexital | Induction of anesthesia | Rapid onset  Short acting  “Prolong on repeated inj.” | Not analgesic  Reduce BP  Reduce RR, TV, apnea, cough, laryngospasm & bronchospasm |
| Opioids; μ, κ & δ receptor “MCQs”  Fentanyl “Potent & for induction&Maintenance”  Morphine “Histamine”  Sufentanil citrate  Alfentanil  Rumifentanil “Ultra short? Ester-linkage”  -Extra-hepatic-renal metabolism > Short-acting | Analgesic | -High potency  -Short acting except morphine  -Profound analgesic  -CV stability  -Reduce emergence phenomenon  -Reversible to Naloxone | -Nausea & slow gastric emptying  Hydrate well to reduce.  -Respiratory depression “High dose”, titrate to prevent but when occur What to do? Assisted ventilation. |
| Ketamine: Contraindications;  CV problem, Glaucoma, High ICP | -Induction for at risk W/ CV problem  **Hypovolemic patient**  -GA/Sedation for child | **-Profound analgesic**  **& amnesia**  **-CV STIMULANT; High HR & BP**  **-Bronchodilator** | Emergence phenomenon “15-65 Y-O”  Bad dream? Give BZs  Increase ICP & IOP  Suppress respiration “Less severe” |
| Propofol: | -Hypnotic/sedative  -Induction & Maintenance of GA  -Sedating intubated | Rapid onset  Short acting **“even with repeated inj.”**  Antiemetic | Injection pain  Reduce HR & BP  Respiratory depression  Involuntary muscle movement |
| Etomidate: | **Induction for CV problem patient** | Rapid onset  Short acting  No CV depression  Minimal respiratory depression | Injection pain “Give lidocaine”  Not analgesic  Involuntary muscle movement  N/V & Hiccups |

***Inhalational anesthetics:***

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| Agent | Advantages | Disadvantages |
| Desflurane;  Outpatient | -Rapid onset & recovery  -Metabolized to least toxic byproduct | -Less volatile? Need vaporizer  -Pungent & irritating to the airway “**Not for extended procedure**”  -High inspired gas > High HR & BP |
| Sevofurane;  Children  Friend of anesthetist | -Rapid onset & very rapid recovery  -Not pungent as Desflurane  -Bronchodilator “Asthma, COPD, Bronchitis” | -CO2 absorbant > **Fluorinated hydrocarbon** > Renal lyase enzyme > **Thioacylhalide**  -Proximal tube necrosis in Rats |
| Isoflurane;  IHD patient | -Peripheral vasodilator “Improve coronary blood flow” | -Moderate solubility **“Delayed recovery**”  -Make heart more sensitive to circulating catecholamines |
| Halothane;  Children | Sweet pleasant smell | If toxic > Arrhythmia  Halothane hepatitis “Rare” |
| Nitrous oxide  The only gas! | Not alone unless full anesthesia is not needed | More N/V  **C.I in air filled cavities “Pneumothorax Air embolus” / Vit.B12 deficiency** |

***Neuromuscular block***: **Uses;** To perform tracheal intubation, facilitate ventilation & Provide optimal surgical condition / **Types;**

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| A) Depolarizing “Succinylcholine”: |
| Structure: Similar to Ach  MOA: Competitive inhibitor  Metabolism: By plasma cholinesterase  Short duration of action, so suitable to facilitate intubation where the muscular relaxation is needed for short time.  ADRs: Facilitation, Muscle pain, Bradycardia, Anaphylaxis, Increase IOP & gastric pressure, Hyperkalemia & Malignant hyperthermia “Dramatic high temperature, acidosis, electrolyte imbalance & shock”  Avoid in ruptured globe Glaucoma, Allergy & Renal disease |

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| B) Non-depolarizing: Competitive antagonist | | | | |
| Agent | **Onset & Duration** | **Metabolism & Excretion** | | **Notes** |
| Pancuronium bromide  “Not used any more” | -1st steroid NMBD clinical use  -Slow onset & long duration  -No Histamine  -**Weak sympathomimetic “Tachycardia”** | -De-acylated in the liver to metabolite with NMB properties.  -Partly excreted unchanged in urine | | -Longer duration in renal and hepatic impairment |
| Vecuronium bromide | -Similar to pancuronium  -Faster onset & short / Intermediate duration  -No Histamine  -No CV effects | -Liver to active metabolite  -Excreted in urine & bile | | Lack of dependence on good kidney function for elimination “Advantage” |
| Atracurium besylate  Not for asthmatic | -Intermediate onset & duration  **-Histamine release**  -No direct CV effect | -Hofmann degradation & ester hydrolysis in plasma  -Metabolite is **laudanosine**  **in case of very slow hepatic metabolism its accumulation cross BBB & induce seizure.** | | Duration of action is independent of kidney or liver function |
| Cisatracurium | -Isomer of atracurium  -No Histamine | -Hofmann degradation  -Less laudanosine formed | | No accumulation in renal failure |
| Rocuronium | -The most rapid onset “60-90 sec”  -Intermediate acting  -No Histamine  -Minimal CV effect | -Metabolized in the **liver**  -Excreted in the **bile** | | High incidence of anaphylactic reaction |
| Anticholinesterase “Neostigmine”: | | | | |
| MOA: Inhibit cholinesterase enzyme at neuromuscular junction | | Reverse the effect of non-depolarizing NMB but no role to reverse the succinylcholine effect! | | |
| ADRs: Miosis, GI upset, Nausea  Increase salivation, sweating & bronchial secretions  Bronchospasm & Bradycardia | | In order to minimize the ADRs, the antimuscarinic should be administered along with it ! | | |
| Antimuscarinic “Glycopyrronium (Glycopyrollate) & Atropine” | | | **Hyoscine**: | |
| The desired effects: Decrease N/V, Salivation & bronchial secretions / Prevent bronchospasm, laryngospasm / Prevent vasovagal attack, bradycardia, hypotension, arrhythmia, cardiac arrest | | | Sedation, amnesia, antiemetic, pupillary dilatation & increase body temperature | |

**Hyoscine & Glycopyrronium cross BBB while atropine no**

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| Complication of anesthesia: | |
| 1. During | **CVS**: Bradycardia, arrhythmia, Cardiac arrest & **hypotension** “Most common”  **Respiratory**: Increased salivation & bronchial secretions, hypoxia, hypercapnia, respiratory depression & aspiration pneumonia / **CNS**: Delirium, convulsion “Midazolam”, Awareness & recall of event “Cardiac surgery & obstetric”, fire & explosion. |
| 1. After | N/V, Atelectasis, pneumonia, liver & kidney damage “Prolong hypotension or hypothermia”  Persistent sedation, Delayed recovery, Delirium & Nerve palsy “Position Ulnar/Common peroneal” |