***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 pupil2nd Loss of corneal & laryngeal reflexes3rd 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 onsetAmnesiaAnticonvulsantMinimal CV effect | Long acting “Diazepam/ repeated inj. Of Midazolam” Not analgesicRespiratory depression |
| Barbiturates; Not for asthmatics Thiopental, Thiamalyl & Methohexital | Induction of anesthesia | Rapid onsetShort acting“Prolong on repeated inj.” | Not analgesicReduce BPReduce RR, TV, apnea, cough, laryngospasm & bronchospasm |
| Opioids; μ, κ & δ receptor “MCQs”Fentanyl “Potent & for induction&Maintenance”Morphine “Histamine”Sufentanil citrateAlfentanilRumifentanil “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 emptyingHydrate 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 BZsIncrease ICP & IOPSuppress respiration “Less severe” |
| Propofol: | -Hypnotic/sedative-Induction & Maintenance of GA-Sedating intubated | Rapid onset Short acting **“even with repeated inj.”**Antiemetic | Injection painReduce HR & BPRespiratory depression Involuntary muscle movement |
| Etomidate: | **Induction for CV problem patient** | Rapid onsetShort actingNo CV depressionMinimal respiratory depression | Injection pain “Give lidocaine”Not analgesicInvoluntary muscle movementN/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;ChildrenFriend 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 oxideThe 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 AchMOA: 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, NauseaIncrease salivation, sweating & bronchial secretionsBronchospasm & 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” |