INTRAVENOUS ANESTHETICS

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Locoregional Anesthesia

- Local infiltration
- Single nerve block
- Plexus block
- Neuraxial block

Signs and Stages of General Anesthesia

Reversable loss of consciousness

Sedation	*Mild CNS depression*. Suitable for surgical procedures not requiring muscle relaxation. Most anesthetics do not produce analgesia.
Delirium	An excited state resulting from *cortical motor depression*. This can be avoided with rapidly acting, potent anesthetics. This stage extends from the loss of consciousness in stage 1 to surgical anesthesia in stage 3.
Surgical Anesthesia	Further subdivided into stages representative of increasing *muscle relaxation*, the final stage is disappearance of muscle tone.
Deep anesthesia and Respiratory paralysis	Generally not desirable

Triad of General Anesthesia

- Need for unconsciousness (Hypnosis)
- Need for analgesia
- Need for amnesia
- (±) Need for muscle relaxation and reduction of certain autonomic reflexes

Anesthesia defined as the abolition of all sensation

Analgesia defined as the abolition of pain sensation

Basic Pharmacology Principals

Pharmacokinetics – often times thought of how the body processes the drugs.

- *Key components include Administration (absorption), Distribution, and drug metabolism and excretion.*

Pharmacodynamics - Is often thought of how a drug causes physiological and pharmacological reactions within the body.

- *Reponses on receptors at the cellular level.*

Basic Pharmacology Principals

Routes: there are various ways of administering drugs GI tract, transdermal, transmucosal, subcutaneous, intramuscular and intravenous.

Most anesthetic drugs use intravenous or inhaled routes.

➢ **First pass metabolism**: Drugs passing through the GI system will also pass through the portal venous system before entering systemic circulation. Consequently, there is extensive metabolism by liver.

Unlike IV administration where it's 100% bioavailable, there is a higher dose requirement for enteric administration of drugs.

Basic Pharmacology Principals

Distribution – systemic circulation to target organs.

- **Free fraction and protein binding**: most drugs are protein bound making them therapeutically inactive, the free portions, are active.

- **Vd** – total dose of drug given divided by plasma concentration.
  Lipophilic drugs VS hydrophilic drugs

- **Redistribution**: some drugs will quickly distribute into certain parts of the body (brain and heart) and slowly into adipose tissue. Once more and more distribution occur into adipose tissue however, equilibrium will force them out of brain and heart, leading to less therapeutic effect.

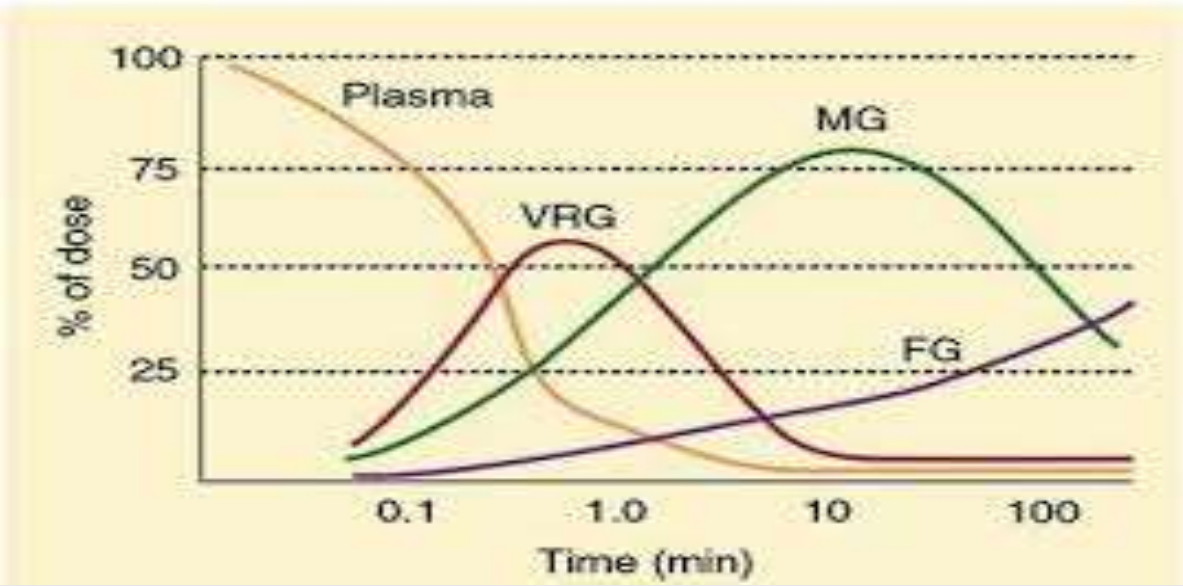
Basic Pharmacology Principals

- Organs are divided according to blood perfusion:
- High- perfusion organs (vessel-rich); brain takes up disproportionately large amount of drug compared to low perfused areas (muscles, fat, and vessel-poor groups).
- After IV injection, vessel-rich group takes most of the available drug
- After highly perfused organs are saturated during initial distribution, the greater mass of the less perfused organs continue to take up drug from the bloodstream.
- As plasma concentration falls, some drug leaves the highly perfused organs to maintain equilibrium.

Basic Pharmacology Principals

- This redistribution from the vessel-rich group is responsible for termination of effect of many anesthetic drugs.

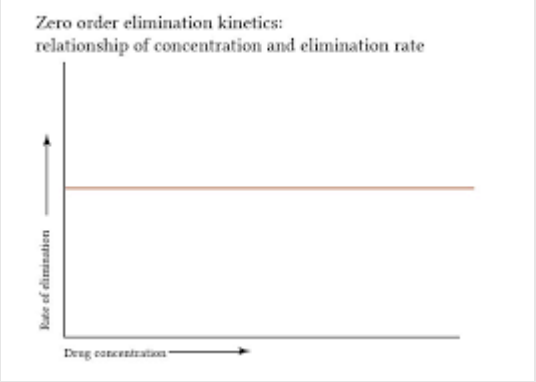
❖**Compartment Model**



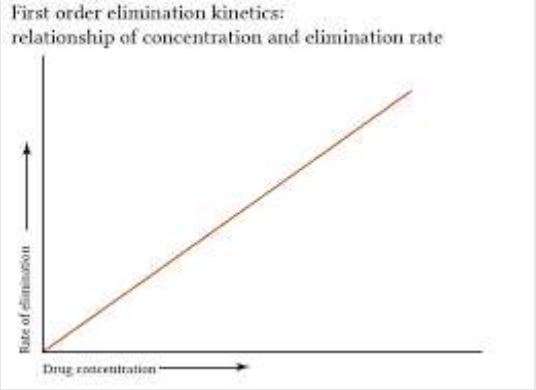
Basic Pharmacology Principals

Metabolism and Excretion – most excretion occurs through liver, kidney and lungs.

- **Zero-order kinetic** – drugs is metabolized at a fixed rate, regardless of concentration



- **First-order kinetic** – most drugs are metabolized through this process, where rate of metabolism is proportional to concentration.
  - Drugs half time – where 50% of drug is eliminated.
  - 5 half-times is equivalent to 96.9% of drug elimination



Basic Pharmacology Principals

Pharmacodynamics

- **Potency**: refers to the dose of the drug required to achieve a therapeutic effect.
- **Efficacy**: refers to the maximum effect achievable with the drug.
- **Toxicity**: Drug toxicity occurs when undesirable side- effects of its administration occur.
- **Therapeutic index**: is the ratio of the dose producing a toxic effect to that producing a therapeutic effect.

IV Anesthetics

MOA

- Commonly used – Propofol, Etomidate, Ketamine, Thiopental (Barbiturate)
  - Either stimulates an inhibitory neurons or inhibits an excitatory neurons.
  - The primary mechanism for **most IV anesthetics** is potentiation of GABA receptors. GABA is the primary inhibitory neurotransmitter in the CNS. Increased chloride conductance across membrane and into postsynaptic neuron promotes hyperpolarization, thus inhibiting neuronal signaling. This has a sedative and hypnotic effect on the individuals.
  - Other IV anesthetic mechanisms –

    Ketamine (exerts effect through inhebiting NMDA receptor) **Dexmedetomidine** (Alpha-2-receptor activation)

Propofol

- Induction Dose: 1.5– 2.5 mg/Kg
- 1% pre-prepared ampules
- Increases binding affinity of GABA with $GABA_A$ receptor.
- Onset: 30-60 secs after administration >> "arm brain" circulation time
- Produced in an 1% egg lecithin emulsion, glycerol and soybean oil (relevant to patient allergies to egg white – not contraindicated with egg allergy).
- Formulation can support bacterial growth – need for good sterile technique
- Highly lipid soluble – only administered intravenously
- Half-life of 2 – 8 minutes
- Rapid hepatic metabolism to water soluble compound and removed by kidneys

Propofol

- Potent cardiovascular and respiratory depressant
- Decreases BP by decreasing cardiac contractility, SVR and preload (inhibition of sympathetic tone and direct vascular smooth muscle effect).
- The most profound cardio depressant of all induction agents.
- Avoid in cases where the patient is hypotensive already or unable to maintain hemodynamic stability.
- In 2/3 of patient is there also pain on injection. Co-administration of 1% lidocaine can lessen the pain.
- Has antipruritic and antiemetic properties – used in TIVA (total intravenous anesthesia) and as background infusion to prevent PONV (post op nausea & vomiting)

Barbiturates

- Most commonly used are thiobarbiturates (thiopental)

  and oxybarbiturate (methohexital)
- Induction Dose: 3 – 5 mg/kg adults
- Each vial contain 0.5 g powder of STP.
- Highly alkaline (pH ~ 10) at 2.5% solution.
- Onset: 30-60 secs after administration >> "arm brain" circulation time
- Enhance $GABA_A$ receptor transmission
- Leads to prolonged cognitive effects compared to Propofol: it decreases cerebral metabolic rate of oxygen (CMRO2), Cerebral blood flow (CBF) and intracranial pressure (ICP).
- Undergo terminal elimination via hepatic metabolism.
- Should not be used in patient with porphyria – will stimulate porphyrin formation and lead to acute crisis.

Etomidate

- Induction dose: 0.2 – 0.3 mg/kg
- 2mg/ml solution
- Can cause irritation and pain on injection.
- Lidocaine pre-administration will help.
- Acts through binding to $GABA_A$ receptors
- decreases CMRO2, CBF and ICP while maintaining good CPP.
- Superior hemodynamic stability compared with other induction agents. Etomidate does not cause vasodilation or myocardial depression
- PONV is common.
- Transiently inhibits 11-B-hyroxlase, an enzyme involved with production of steroids – can cause adrenal suppression.
  - Inhibition lasts for 4 – 8 hours, worse with infusions

Ketamine

- Dose: 1 to 2 mg/kg IV .

  The IM induction dose is 4 to 6 mg/kg.

- Several routes of administration: IV, IM, Oral, Rectal, epidural and intrathecal
- Mechanism through NMDA (N-Methyl-D-aspartate) receptor antagonism.
- Causes analgesia by blocking pain signals at spinal cord but also disassociating the signal between thalamus and limbic system.
- Dissociative amnesia – patient appear conscious (eye open, staring) but unresponsive to sensory input (pain, verbal, stimulus)
- Can causes unpleasant emergence reactions with hallucination and fear.

Ketamine

- Stimulates sympathetic nervous system
- Has minimal respiratory depression
- Causes potent bronchodilation
- Increases CBF, CMRO2, ICP.
- Direct myocardial depressant but indirectly increases catecholamines resulting in increased blood pressure, heart rate and cardiac output.
- Relative contraindication in patients with space-occupying CNS lesions

Dexmedetomidine (Precedex)

- Highly selective alpha-2 adrenergic agonist
- Sedation and analgesia without much respiratory depression
- Half-life of 2 hrs.
- Dose:
  - Loading dose: 0.5 – 1 mcg/kg over 10 minutes
  - infusion dose: 0.2 – 0.7 mcg/kg
- Has sedative, analgesic, sympatholytic, and anxiolytic effects
- Sedation for awake fiberoptic intubation, regional anesthesia or as an adjunct to general anesthesia. In ICU, to wean patients off ventilator

Benzodiazepines

- Commonly used benzos are: Midazolam , Diazepam and Lorazepam
- All benzos have anxiolytic, amnestic, sedative, hypnotic, anticonvulsant properties. NOT analgesic.
- Bind to same $GABA_A$ receptors as barbiturates but at different site on receptor
- Produce mild respiratory, cardiovascular and upper airway reflex depression
- Usually given as premedication, sedation and anxiolysis before GA
- Half-life of 3 hrs
- Dose for Midazolam
  - Premedication: 0.04 – 0.08 mg/kg IV (1-2 mg)
  - Induction dose 0.1 – 0.2 mg/kg IV
- Unlike Propofol and barbiturates, sedation can be reversed by administration of flumazenil – specific competitive antagonist with high affinity for benzo receptors

	CVS			RS	CNS		
	HR	SVR	MAP	Ventilation	CBF	CMRO2	ICP
Barbiturate	+	-	--	---	---	---	---
Propofol	0	--	---	---	---	---	---
Benzodiazepines	+	-	-	--	--	--	--
Etomidate	0	0	0/-	-	---	---	---
Ketamine	++	0	++	0/-/+	+++	+	+++

Drug	Speed of Induction and Recovery	Pain on injection	Delirium	PONV	analgesia
Thiopental	Fast Accumulation occurs, giving slow recovery	No	-	0	-- antanalgesic
Etomidate	Fast onset Fairly fast recovery	Yes	-	+	0
Propofol	Fast onset, Very fast recovery	Yes	-	--	0
Ketamine	Slow onset	No	++	++	++
Midazolam	Slower than other agents	No	-	0	0

The ideal intravenous anesthetic agent

- Rapid onset
- High lipid solubility
- Rapid recovery, no accumulation during prolonged infusion
- Analgesic effect
- Minimal cardiovascular and respiratory depression
- No emetic effects
- No pain on injection
- No excitation or emergence phenomena
- No interaction with other agents
- Safe following inadvertent intra-arterial injection
- No toxic effects
- No histamine release /No hypersensitivity reactions
- Long shelf-life at room temperature

QUESTIONS !!!