

## **GENERAL ANESTHETIC AND LOCAL ANESTHETIC AGENTS**

The basic elements are unconsciousness, analgesia, inhibition of noxious reflexes, skeletal muscle relaxation. Defined Progressive reversible intoxication of the central nervous system. With the exception of dissociative anesthesia, the effect on the C.N.S. can be divided as follows.

- Stage I Voluntary excitement
- Stage II Voluntary excitement
- Stage III General Anesthesia

Plane 1 Light anesthesia

Plane 2 Medium anesthesia

Plane 3 Deep anesthesia

Stage IV Over dosage (Medullary Paralysis)

**Hypnosis:** Loss of consciousness

**Hypovolemia:** Decrease in Plasma volume

**Induction:** Administration of anesthetic agent to cause an animal to lose consciousness.

**Maintenance:** Administration of anesthetic agent to maintain general anesthesia.

## **MONITORING**

This is observation of signs of anesthesia, particularly movement, righting reflex, response to voice, palpebral reflex and autonomic responses (HR, BP e.t.c.)

### **Pre medication**

Administration of tranquilizer, sedatives, benzodiazepines or opioid before of induction of general anesthesia.

### **An ideal intravenous anesthetic agent**

- Water Soluble stable to light
- Small volume
- Small individual variation
- Safe therapeutic ration
- Onset in one arm-brain circulation time.
- Short duration of effect
- Rapid in activation and rapid recovery
- No histamine release

- No local toxicity or altered organ function.

### **Anesthesia and Agents inducing Anesthesia (Anesthetic Agents)**

Anesthesia: the loss of all sensation. May be described as local (affecting a small area) or regional or surgical (accompanied by unconsciousness)

We have general and local anesthetic agents

#### **A. General Anesthetic Agents**

##### **1. Intravenous anesthetic agents**

###### **a. Barbiturates**

- i. Long acting barbiturates (8-12hrs), e.g. Phenobarbital
- ii. Short- Acting barbiturates 45 minutes – 1.5hrs, e.g. Pentobarbital
- iii. Ultra short- Acting barbiturates 5-30minutes, e.g. thiopental

##### **2. Dissociatives**

Ketamine

Tiletamine

##### **3. Alkylphenol**

Propofol

##### **4. Carboxylated imidazole**

Etomidate

##### **5. Steroids Anesthetic Agents**

Alphadalone/Alphaxolone

##### **6. Muscle Relaxants**

Gaifenesin

#### **Inhalation Agents:- e.g.**

Isoflurane

Halothane

Nitrous- oxide

Sevoflurane

#### **Local Anesthetics**

1. Procaine, lidocaine, bupivacaine, tetracaine, cocaine.

#### **Barbiturates**

##### **1. Chemistry**

- i. Derivatives of barbituric acid (non-hypnotic).
- ii. White, odorless, bitter crystals or powder.
- iii. Stable in air, slightly soluble in water
- iv. Available in clinical practice as the salt by addition of Na or C<sub>2</sub> in lightly alkaline structure-activity relationship.

#### **Barbituric acid nucleus**

### **Long-Acting Barbiturates** (Phenobarbital) 8-12hrs

Propriety name Luminal and numerous other names used as epileptic seizures.

Administered oral route

### **Short – Acting Barbiturates** ( $3/4 - 1\frac{1}{2}$ hrs)

Nebutal

Route: Intravenously, Intrapentoreally

Used to control seizures and used as an anesthetic agent in earlier days of vet practice

Now or today is used to control seizure and euthanasia

### **Ultrashort- Acting Barbiturates**

- Very Alkaline (Especially at higher concentration)
- It must be given I.V to avoid necrosis
- It is rapidly redistributed in to fats stores of the body within 5-3 minutes.

*Note: care must be taken when administered to a thin animal because it lacks fats.*

- Use sterile water for injection to dilute drug because solution wit electrolyte hasten PPt formation

*In administration caution must be taken when admonishing too slowly I.V. it causes CNS.*

### **Excitement**

- To administer give  $1/3 - 1/2$  of calculated dose should be given rapidly to avoid excitement phase. The remainder of the dose is administered in increments until the desired effect is achieved.

### **Mechanism of action of Barbiturates**

- It inhibits glutamate activity
- Acts on the GABA eragic receptors

### **Pharmacokinetics**

Distribution of Barbiturates

1. Distribution to tissue speed according to density of blood supply adequacy cardiac output and tissue perfusion.
2. Volume of distribution hypovolemia dehydration old age obesity this the risk of overdosage is increased in these patients.

3. Protein binding: hypoproteinemia, specifically decreased serum albumin, result in increase availability of thiopental.
4. Ionization- in thiopental (PKa 7.6), acidosis result in more non ionized drug, while alkalosis result in ionization therefore if the animal is having acidosis this result in deeper plane of anesthesia or from the clinical perspective less drug is needed to produce anesthesia in an acidotic patient.

#### **D. Fate**

Liver biotransformation of the drug and this is slowed by hypothermia (when animal gets cold). Consequently pentobarbital is rarely used in clinical anesthesia of dogs and cats.

#### **Caution**

Pentobarbital is never used in **horses** and **cattle**

*As much as 30% of thiopental may remain in tissues after 24hrs with no signs of depression care must be taken because it assumes clinical importance if the animal is re-anesthetised with 24hrs*

- Chloramphenicol prolongs sleeping time from barbiturates.

#### **Pharmacologic Effects**

##### **A. Central Nervous System**

- Decrease intracranial pressure
- Administered of glucose to pentobarbital – may result in deepening

##### **B. Cardiovascular (Thiopental)**

- Venous dilation
- Decrease central catecholamine out flow
- Decrease cardiac output, increase heart rate from baroreceptor reflex, decreased mean arterial pressure or unchanged.

#### **Clinical Use**

1. an average mg/kg dose rate is known for each species of animal and for specific pre anesthetic sedation regimens. This dose is known as “Calculated dose” and is drawn up into a syringe during preparation of anesthesia.

2. Usually, about one half of the calculated dose is injected rapidly to ensure sufficient C.N.S depression and avoidance of stage II involuntary stage.

### **Dissociative anesthetics**

Dissociative anesthesia resembles a cataleptic state in which the eyes remain open and although non-responsive, the patient may appear wakeful. There is varying degree of increase muscle tone and spontaneous limb movements are present.

- \* Ketamine hydrochloride
  - \* Tiletamine hydrochloride
- Phencycline (No longer Marketed).

### **Ketamine**

#### **Chemical Properties**

1. Racemic mixture of optical isomers
2. Water soluble
3. The 10% solution has a pH of 3.5 (Time very irritant in muscle)
4. High lipid solubility, 5-10 times that of thiopental

#### **Mechanism of Action**

- Ketamine may bind to central and peripheral opioid receptors
- Interference with the membrane effects of the excitatory neurotransmitter glutamic acid by block of NMDA (N-Methyl-D-aspartate) receptors.

Previously this group is believed to cause functional and electrophysiological dissociation between the thalamocortical and limbic systems.

#### **Pharmacokinetics of Ketamine**

- Ketamine would have high bioavailability following I.V. or I.M administration. When given orally higher doses are required
- Plasma Ketamine concentration following a bi-exponential decline
- Awakening from Ketamine occurs as CNS concentration of Ketamine decreases, by redistribution from the central to peripheral compartments
- Clearance is achieved by hepatic biotransformation and renal elimination.
- Nor-Ketamine is a metabolite and it has  $\frac{1}{3}$  of the anesthetic potency of Ketamine

- In dogs and cats metabolism and excretion plays a part in terminating the action of Ketamine where as in horses recovering is almost entirely due to redistribution of drug from central to peripheral compartment.

## Pharmacologic Effect

### A. On the C.N.S

- Ketamine induces consistent changes in electroencephalogram decreased alpha wave activity increases that and delta activity.
- It recommended to use Ketamine in combination with another drug because the administration of this alone may cause seizure in dogs and horses.
- Intracranial pressure is increased by administration of Ketamine this may be increase due to PaCCO<sub>2</sub> from respiratory depression

**Note:** Ketamine is contraindicated in patients with cerebral trauma or intracranial space occupying lesions.

- Clinical signs that may represent hallucination in cats and dogs when recovering from Ketamine anesthesia.
- Effect of Ketamine diminishes more rapidly in horses than dogs and cats.

### B. Respiratory system

Ketamine is amid respiratory depressant.

### C. CVS

Ketamine causes significant ↑ HR    ↑ MAP    ↑ CO

### D. Temperature

Ketamine Temperature (rectal)

- Causes Salvation especially in cats

### Clinical Use of Ketamine

The drug is used in cats, dogs, goats, calves

The drug is also used in pigeon and parrots in avian surgery

The drug combination use in cats, dogs and foals

- (a) Acepromazine and Ketamine
- (b) Diazepam or midazolam and Ketamine
- (c) Xylazine and Ketamine

(d) Telazol and Ketamine

### **In Horses**

Xylazine, diazepam and Ketamine

In Swine

\* Acepromazine and Ketamine

\* Xylazine and Ketamin

### **Propofol**

This belongs to the class alkylphenol. It produces rapid induction and rapid recovering with cumulative effect. It may cause significant cardiovascular depression.

### **Chemical Properties**

A. Formulated in an white, oil-in-water emulsion with soybean oil, glycerol and egg lecithin.

B. pH 7.0-8.5

### **Pharmacokinetics**

- 2 distribution Phases is associated with transfer of drug from vessel-rich to vessel- poor in I.V administered single dose
- Extensive hepatic metabolism by conjugation to inactive metabolites which are excreted by the kidney. There is also extra hepatic metabolism.
- Termination of effect due to extensive redistribution from C.N.S and to high metabolic clearance.
- The drug is recovered in urine by 24hrs by the 5<sup>th</sup> day after administration more than 90% of the drug is excreted.

### **Pharmacologic effects**

#### **A. C.N.S**

1. Rapid onset of anesthesia- less than 60 seconds
2. Decreases cerebral blood flow and intracranial pressure.

#### **B. Respiratory**

1. Transient apnea after I.V bolus injection. Slower injection of (1-2min) may avoid apnea.

#### **C. Cardiovascular**

1. Mean arterial pressure and cardiac output decreased
2. Increased myocardial sensitization to Catecholamines.

### **Clinical Use**

- Used in dogs and cats frequently
- Used as induction anesthesia to inhalant anesthesia agents. It is best used when a pre-anesthetic sedation is used.
- It can be use in maintenance of anesthesia by continuous intravenous infusion.

### **Etomidate**

This belongs to the class carboxylated imidazoles, is a short acting non- barbiturate anesthetic agent with minimal cardiovascular depression when compared to thiopental.

### **Disadvantages of drug**

- Little or no analgesic activity.
- Suppresses adrenocortical activity.
- It has adverse effects (Myoclonus, excitement, vomiting) when is used alone.

### **Chemical properties**

- Water soluble at an acid PH and lipid soluble at physiologic PH.
- Commercially prepare in propylene glycol-solution.

### **Pharmacokinetics**

#### **Distribution**

- Etomidate penetrates the brain rapidly, peak concentration within 1min after I.v injection.
- 76% bound to plasma albumin this implies in hypoproteinaemia would lead to free form of the drug and this brings about toxicity.
- Vd is large indicating considerable tissue uptake.
- Return of consciousness, after single I.v dose is mainly due to redistribution of drug.

#### **Fate**

1. Etomidate is rapidly biotransformed plasma and hepatic hydrolysis take place in rats cats.
2. Hydrolysis of the ethylester side chain tacts carboxylic acid ester, resulting in a pharmacologically inactive compound.

Ethylester side chain  $\longrightarrow$  carboxylic acid ester



## Hydrolysis

(inactive compound)

- Hydrolysis take place by hepatic microsomal enzymes and plasma esterases

### Pharmacologic effects

#### A. CNS

Depression caused by cerebral vasoconstriction this decreasing cerebral blood flow and intracranial pressure etomidate acts like GABA.

#### B. Respiratory

Significant decrease in respiratory rate.

#### C. Cardiovascular

Cardiovascular function preserved with little haemodynamic change when used to induce anesthesia.

D. Excitement, pain on injection, myoclonus and vomiting during induction of anesthesia.

**Clinical use:** Used in humans and dog

- Drug of choice in patients with cardiac disease that cannot tolerate myocardial depression (cardiomyopathy).
- Premedication with tranquilizer, sedative or opioid recommended to decrease frequency of toxicity.

### Steroid anaesthesia. Examples Alphadione/ Alphaxalone

#### Advantages

- Wide therapeutic index
- Minimal cumulative effect
- Excellent muscle relaxation
- Minor Cardiovascular and
- Respiratory depression
- No tissue damage

#### Disadvantage

- Histamine release
- Not used in dogs
- Large volume i.m

- Can not be given with barbiturates.

## **Pharmacokinetics**

### **Distribution**

1. Low degree (17-25%) Protein binding compared with other agents.
2. Return of consciousness principally due to redistribution into tissues.
3. The drug appears in bile, in gut human by 3 minutes suggestive of enterohepatic circulation.
4. Duration of anesthesia is dose-dependent but in cats a “calculated dose”.

### **Fate**

1. Metabolism by hepatic microsomal enzymes, especially glucuronyl transferase.