

COURSE CODE:	VPC 401
COURSE TITLE:	SYSTEMIC DRUGS AND THEIR ACTIONS
NUMBER OF UNITS:	NUMBER OF UNITS: 2 UNITS
COURSE DURATION:	TWO HOURS PER WEEK

COURSE DETAILS:

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COURSE CONTENT:

Drugs acting on the nervous, musculoskeletal, gastrointestinal, urinary, respiratory, reproductive, endocrine, cardiovascular systems and anti-inflammatory drugs.

COURSE REQUIREMENTS:

This is a compulsory course for all veterinary medical students in the University. In view of this, students are expected to participate in all the course activities and have minimum of 75% attendance to be able to write the final examination.

READING LIST:

- Aliu, Y.O (2007) Veterinary Pharmacology (1st edition).
- Boothes M. (2001). Veterinary Pharmacology and Therapeutics for small animals.
- Nicholas H.B. (1988). Veterinary Pharmacology and Therapeutics. IOWA University Press.
- Onyeyili, P. A. and Egwu, G. O. (1995). Chemotherapy of African Trypanosomosis: Historical perspective. *Pot Abstracts* 19(5): 230-241.
- Wanamaker B.P and Kathy L.M (2009). Applied Pharmacology for Veterinary Technicians 333 -335.

DRUGS ACTING ON THE NERVOUS SYSTEM

ANTI-EPILEPTIC DRUGS

General Principles of Treating Epilepsy, Seizure or Convulsion

1. Try to identify the type of condition and specific classification take good history.
2. Remember that primary epilepsy can not be cured but could be managed.
3. When seizure is in progress and it is prolonged, it is therefore life threatening, use emergency action (approach) i.e. i.v. administration of drugs.
4. Seizures that are periodic, recurring use preventive oral medication.
5. Oral preventive therapy often must be titrated to the individual patient and reviewed regularly adjusting dose and hence controlling the disease.

Cases of Epilepsy in Veterinary Medicine

- Animals that suffer epilepsy: Canine *spp* (Dogs). Familiar or idiopathic type is common in exotic breeds of dog e.g. pug, Labrador, German shepherds, Golden retrievers etc.
- In cats (Felines): Korat cats due to absence of cerebral gyri (Lissen Cephalo) results in seizures.
- Equines: Benign epilepsy seen in young foal particularly Arabian horses.
- Bovine: Brown Swiss, Swedish Red Cattle, *spp* etc. This familiar listeriosis disease.
- Caprine/Goats: Cowdriosis, caused by *Cowdria ruminantium*.
- Gerbils: also suffer from epilepsy.
- Anti-convulsant: These are drugs used to treat convulsive conditions of seizures.
- Antiepileptic drugs: these are drugs used to manage epilepsy or seizures..

Drugs requirement for treatment of epilepsy

Maintenance therapy –

1. Fairly long duration of action.
2. Metabolic tolerance from liver enzyme induction should not enhance drug clearance as to render the therapy impracticable.
3. Good oral absorption and subsequent passage of blood brain barrier.
4. Effectiveness of sub-sedative dose rate.
5. Absence of major side effect.

Status epilepticus

1. Effective, centrally acting muscle relaxant properties.
2. Should have rapid onset of action but long duration of action is not important.
3. Available in a formulation suitable form for intravenous or i.m. inj.
4. Minimal effects on cardiovascular and respiratory system.

First-line of Anticonvulsant Drugs.

- Phenobarbital.
- Potassium bromide (KBr)
- Sodium bromide (NaBr)
- Diazepam

Second-line (add on) Anticonvulsant Drugs.

- Clonazepam.
- Clorazepate
- Felbramate
- Gabapentin
- Levetiracetam
- Topiramate
- Valproic acid
- Zonisamide

Drugs Used to treat status epilepticus

- Diazepam 0.5-1.0mg/kg i.v. bolus can be repeated 2-3 times at interval of 5-10mins
- Phenobarbital 2-4mg i.v. bolus can be repeated 20-30min interval to dosage of 20mg/kg.
- Pentobarbital 2-15mg/kg i.v. to effect stoppage of motor activity.
- Propofol 1-2mg/kg i.v. to stop motor activity at 0.1-0.6mg/kg/min.

Mechanism of action of drugs used as Anticonvulsant and Anti-epileptic drugs.

Drugs used in seizure reduction act by the following means:

- Block the initiation of electrical discharge from the focal area.
- Or more commonly, prevent the spread of abnormal electrical discharge to adjacent brain areas.
- This is done by blockade of voltage-gated channel (Na^+ or Ca^{2+})
- Enhancement of inhibitory GABAergic transmission.
- Interfering with excitatory glutamate transmission.

Drugs contraindicated for epilepsy patients.

1. Fluorinated quinolones
2. Lidocaine.
3. Methyl xanthines
4. Morphine sulphate
5. Chloramphenicol
6. Metoclopramide

Phenobarbital – Mechanism of action

- Increases the threshold required for seizure discharge and decreases the discharge to surrounding neuron.
- Acts on the GABAergic receptors.
- It inhibits glutamate activity.

Disposition & Pharmacokinetics

- It is a weak acid (pka 7.3) absorbed orally.
- It reaches peak plasma concentration 4-6hours after.
- It has half life of $1.27 + 0.21$ hrs.

- It is bounded to serum protein in dogs.
- The drug is metabolized via microsomal enzymes by oxidative hydroxylation.
- It eliminated in the blood via conjugation of the hydroxyphenobarbital with glucoronide.
- It is eliminated renally.

Preparations:

Oral or injectable preparations

Oral tablets contain 0.25, 0.50 or 1grain (15, 30 and 65mg) respectively.

Clinical Use

- It is the widest used anti epileptic drug because it has wide spectrum of activity in different convulsive seizures.
- Clinically, it is used with a loading dose of 12mg/kg i.v.
- It could be given four to six equal hourly doses.
- It could be given in combination with i.v. diazepam to prolong the control of seizures the phenoherbital should be administered 1/m this is to avoid respiratory and cardiovascular depression.

Dosage and Frequency:

Dog – 2-4mg/kg P.O. BID (twice daily) up to 10mg/kg BID.

Given to achieve therapeutic concentrations of 20mg/ml.

Side Effects:

1. It might affect behavior of animal, polyphagia, polydispsia, polyuria.
2. Bone marrow dyscrasias – It can cause allergic reactions in dogs, Panyctopenia, neutropenia.
3. Thyroid – It affects the thyroid gland to cause hypothyrodism.
4. Hepatotoxicity may occur (serum alkaline phosphotase, Alanine amino transminases etc might increase.
5. Acute toxicosis might affect respiratory centres depressing respiration.

Treatment of Acute Phenobarbital Toxicosis.

1. Dogs could tolerate marked overdose (Concentration of 150mg/ml)
2. Artificial respiration oxygen should be provided doxapram and analeptics should be provided to stimulate the respiratory centre.
3. Alkalinization of urine accelerates renal excretion of Phenobarbital.

Bromide (Na, K and NH₄) – Mechanism of Action

- It is not fully understood in earlier years. But it is believed that there is replacement of the negatively charged chloride with bromide the neuron becomes hyperpolarized (RMP becomes more negative in relation to the threshold potential).
- It is also said that the mechanism of action is related to the plasma concentration.

Pharmacokinetics

- It has a half life of 21-24days.
- It steady state cannot be achieved if or approximately 3-6 months.
- Distribution is to extracellular fluid, but yet penetrates the CNS.
- It is reabsorbed by the kidney slowly thus, due to its marked reabsorption
- Increase in dietary salt would increase the rate of elimination of the drug.
- Faster elimination takes place in cats than dogs.
- $T_{1/2} = 10$ days in cats.
- Steady stage in 6 weeks.

Side Effects:

Adverse reactions to bromide tend to be dose dependent.

- Mix recently adverse dry effect in cats include bronchial asthma.
- Experience show the toxicity is related to its anticonvulsant effect which include ataxia, grogginess, hyperactivity.
- Sedative effect may take 3 months to manage.
- Pruritic skin lesions may occur (glucocorticoid may be used to control pruritus) caused by bromide.
- Like other anti-convulsants, it tends to increase the appetite of dogs.
- Hypertonicity due to effect of the salt might cause gastric irritation and vomiting.
-

Note: NaCl can be used to treat acute bromide toxicity.

Chemical Properties

1. Diazepam is dissolved in organic solvents e.g. propylene glycol because it is insoluble in water.
2. Viscid solution with a pH of 6.6-6.9.
3. Dilution with water or saline causes cloudiness, but does not alter the potency of the drug.
4. I.M. or I.V. injection. May be associated with signs such as pain.

Pharmacokinetics and fate

Distribution –

Extensive binding (96-98%) to plasma proteins.

In dogs, it has elimination half life of 77min.

Elimination is larger in geriatric patients.

Metabolism –

Oxidation by hepatic microsomal enzymes. Metabolites excreted in urine as glucuronide conjugates.

Somnolence after diazepam may persist due to active metabolite and enterohepatic recirculation.

Cimetidine H₂ receptor antagonist interfere with metabolism of diazepam this prolong the effects of diazepam.

Mechanism of Action –

It increases the availability of inhibitory neuro-transmitters (glycine). This result to anti-anxiety effect of skeletal muscles and relaxation.

It facilitates the inhibitory neurotransmitter GABA (Gamma Amino Butyric Acid) this result to sedative effect.

Pharmacologic Effects

Central nervous system

1. Anti convulsant effect
2. It has very little effect of tranquilizing effect in dogs, cats or horses when administered alone.
3. Effect in sick patient varies from mild to profound sedation

4. Low dose of diazepam can be used to stimulate appetite in some inappetence patient.

Respiratory System

1. Minimal in healthy patient when given done
2. When combined with other drugs anesthetic agent this result to respiratory depression.

Cardiovascular System

1. When given, in low or moderate doses it brings about minimal change in cardiac output and arterial pressure. In large doses, it causes decreased mean arterial pressure.
2. Heart rate sometimes is decreased.

Diazepam is a benzodiazepine

The Clinical Use

Dosage:- 0.5 – 2mg/kg in dogs, 0.25 – 2.0mg/kg in cats Po BID-TID

Route of administration: 1m or 1v orally (Tid)

1. Benzodiazepines are rarely used alone in healthy patient.
2. Diazepam has aesthetic use
 - It may be injected immediately before, or mixed with, Ketamine in healthy or sick dogs, cats, horses or small ruminants. ‘
 - It is used as pre medication agent.

Diazepam Toxicity

It could be reversed by flumazenil which bind competitively, reversibly and specifically to the same receptor sites in C.N.S. So flumazenil could be used in case of toxicity of the drug due to overdose.

Clonazepam and other Benzodiazepines (Clonazepam, Lorazepam, Clorazepate)

This is also a benzodiazepine used for management of epilepsy. Clorazepate and Clonazepam are used for chronic treatment in man where as diazepam and lorazepam are drugs of choice in the acute treatment of status epilepticus. Clonazepam suppresses seizure spread from the epiletogenic focus and is effective in absence and myoclonic seizures. Clorazepate is effective in partial. Seizures when use in conjunction with other drug e.g. Phenobarbital.

Pharmacokinetics of Clonazepam

- The drug is dose- dependent (Zero order)
- ($t_{1/2}$) Half life is ranging from 1-6h.
- Bioavailability with oral dosing depends on the physical state and formulations containing macronized drug. It is possible to maintain plasma concentration within arrange which should be clinically effective wiht4 oral dosing three times daily.

Clinical Use

It is used in emergency treatment of status epilepticus

Dosage and Frequency

0.1-0.5mg/kg, P.O. BID-TID

Side Effects

- Diarrhea may sometime occur
- Withdrawal signs if the drug is stopped abruptly

FELBAMATE

Mechanism of Action

- Inhibition of excitatory signals or inhibition of sodium influx
- Potentiation of GABA receptors mediated Chloride.

Pharmacokinetics

- Felbemate is well absorbed after oral administration
- In young dogs or pediatric animals bioavailability is as little as 30% of that in adult dogs.
- Drug is metabolized via hepatic metabolism to metabolites that are inactive

$t_{1/2}$ is 4-8hrs in adult dogs

$t_{1/2}$ is puppies or pediatric patients 2.5hrs

Dosage

Ranges from 15mg/kg divided twice daily to 30mg/kg

Peak concentration of the drug is achieve in dogs when given 60mg/kg

Side effects

- * Sedation * Polyuria, Polyphagia, Polydipsia
- * Aplastic anaemia due to bone marrow depression

Clinical Use

- The drug is very safe
- It has broad mechanism of anti-convulsant activity
- It is very useful in monotherapy
- It is proved to be efficacious for treatment of generalized seizures.
- In dogs in combination with Phenobarbital can be used to control refractory epilepsy.

Recommendation when using the drug

- Complete blood count and liver should be monitored

GABAPENTIN

Mechanism of Action

- Promoting the release of GABA, although the actual mechanism of release is not known.

Pharmacokinetics

- It is well absorbed after oral administration absorption appears to be dose dependent.
- The antiepileptic effects last longer than anticipated this is based on the half life it reaches steady state in 24 hours to 48 hours.
- The drug is eliminated entirely by renal elimination. This avoids hepatotoxicity and drug interaction.

Dosage and Administration

10-30mg/kg orally every 8 hours (Tid) 60mg/kg (Tid)

Doses are usually higher doses

Side Effects in dogs

Mild dizziness, nausea and vomiting have occurred in humans.

ZONISAMIDE (Zonisamide).

Mechanism of Action

- Blockage of both voltage-gated sodium channels and T-type calcium current
- It also acts by enhancement of GABA receptor

Pharmacokinetics

- Orally active and well distributed throughout the body
- It has a long life (50-60hrs) when administered without enzyme inducers.
- If it is given with enzyme inducers it shortens its half life to 25-30hrs.

The parent compound (thirty percent). Its N-acetyl metabolite (twenty percent), and its glucuronide (fifty percent) are excreted in the urine.

Adverse Effect

- * Typical C.N.S adverse effect
- * May cause kidney stone
- * Loss of appetite
- * Sedation

Clinical Use

- * For focal and generalized seizures

Dosage: 4-8mg/kg day or 10mg/kg BID

LEVETIRACETAM (lee vet ye RA Se tam).

Mechanism of Action

Its mechanism of anticonvulsant action is unknown

Pharmacokinetics

- The drug is well absorbed orally
- Excretion is urinary with most of the drug 66-70 being unchanged
- There is no hepatic metabolism
- It has a remarkable free pharmacokinetic drug interaction for this reason is a good choice for adjunctive therapy.

The Side Effects

- Irritation, restlessness, vomiting and ataxia at dosages as high as >400mg/kg.

Dosages and Frequency

In drugs 20mg/kg P.O. TID,; 500-400

$t^{1/2} = 4-10\text{hrs}$

Steady State of drugs

2-3 days

PHENYTOIN (diphenyl hydration)

Is no longer recommended for use in dogs, cats or foals due to undesirable pharmacokinetics properties. In dog too rapid metabolism in dogs, this reduces its effectiveness.

In Cats too slow metabolism in cats, this increases the risk of toxicity (Salivation, Vomiting, Weight loss).

In foals it has erratic plasma concentration it is carefully given at 15-40mg/kg, P.O.TID.

Dosage: It can be given I.V 5.10mg/kg, with subsequent administration at 1-5mg/kg, I.V, I,m or P.O every 2-4hrs for 12hrs.

Mechanism of Action

- Blocks voltage-gated sodium, channels by selectively binding to channels in the in active state and slowing its rate of recovery.
- It also blocks voltage- dependent-calcium channels and interferes with the monoaminergic neurotransmitters.

TOPIRAMATE (toe peera mate Pronounced)

(its effectiveness is not yet know)

Mechanism of Action

- Blocks voltage dependent, use-dependent sodium channels
- Shown to increase the frequency of chloride channel opening by binding to the GABA receptors.
- Prevents phosphorylation of variety of proteins, including anti- epileptic targets.
- Calcium current (Possess High- Voltage) (L Type) are reduced.

Pharmacokinetics

- Well absorbed orally
- Oral bioavailability of 100%
- Peak concentration occurs in about two hours
- 30% of each dose is metabolized.

$t^{1/2}$ 20-25hrs

Adverse Effects

- C.N.S and git disturbances
- Impaired concentration
- Dizziness
- Ataxia
- Nervousness
- Confusion
- Nausea, Weight loss

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 C₂ 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 ($\frac{3}{4}$ – 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 $\frac{1}{3}$ - $\frac{1}{2}$ 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 neurotransmitters 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 PaCCo₂ 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 anHITE, oil-in-water emulsion with soyabean 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 in active 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 5th 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 Cathecolamines.

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.

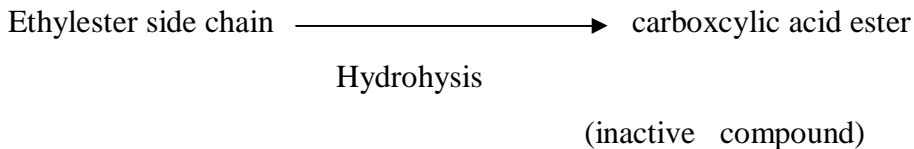
Pharmacokinetics

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.



- 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.

REQUIREMENTS OF AN IDEAL LOCAL ANESTHETIC

The ideal local anaesthetic would possess many desirable properties. It should produce available paralysis of the sensory nerves but not of other tissues

1. The agent should have non-addictive properties.
2. It should be readily soluble and stable in water.
3. The local anaesthetic should possess a pH neutrality and be nonirritating to the tissues.
4. It should possess a minimum of systemic local, toxicity, as evidenced by absence of tissue damage at the injection site
5. The local anesthetic should be absorbed slowly to minimize danger of systemic, toxicity and to prolong the effect at the site of injection.
6. After systemic absorption the compound should be readily and promptly detoxified.
7. It should be compatible with adrenaline so that it anaesthetic vasoconstrictor
8. There should be no hyperaesthesia following the recovery of sensation by the tissues.
9. The local anaesthetic should withstand heat sterilization and be relatively inexpensive.

Mechanism of Action:

Local anaesthetics are generally water soluble acid salts. When these salts are injected into the slightly alkaline body tissues they appear to hydrolyze slowly releasing the alkaloidal base, which then acts upon the nerve tissue.

Generally, local anaesthetics prevent the generation and conduction of nerve pulses. Their site of action is the cell membrane and the block they produce is the result of interference with changes in membrane permeability to potassium and sodium ions and possibly calcium ions. These permeability changes are responsible for the rising and falling phases of the action potential and they follow depolarization of the membrane. In the presence of a local anaesthetic, the electrical excitability of the tissue gradually decreases until eventually, complete block ensues.

How local anaesthetics affect the transient changes in ion permeability is unknown but the potency of these compounds is matched by their ability to increase the surface pressure of monomolecular lipid films. It has been suggested that the anaesthetic “squeezes” the lipid molecules closer together. In the lipid membrane layers of nerves this could have the effect of closing membrane “pores” so reducing ionic permeability. This would have the effect of stabilizing the membrane and reducing its excitability.

Pharmacological Actions

In addition to their action in blocking conduction in nervous tissue, the local anaesthetics interfere with the function of all organs in which the transmission of electrical impulses occurs. The most important effects are on the CNS and heart.

Central Nervous system – Most local anaesthetics stimulate the CNS and overdose may lead to tremors, restlessness, and convulsions. Central depression may occur later and death may result from respiratory depression. The stimulant action may be the result of a block in vulnerable central inhibitory pathways. Although all local anaesthetics cause stimulation, cocaine is unique in having a powerful effect on the central cortex and it may be this which makes cocaine addictive, synthetic local anaesthetics have less stimulant action on higher centres and do not cause addiction.

Cardiovascular system – If given systemically, local anaesthetics have quinidine-like action on the myocardium and reduce its excitability and force of contraction: they also prolong the refractory period and slow conduction. These effects cannot easily be taken advantage of because the drugs are rapidly destroyed and their CNS effects usually predominate. All local anaesthetics except lignocaine and cocaine produce vasodilatation by a direct action on the arterioles.

Fate and Metabolism of local anaesthetics

All local anaesthetics are broken down in the liver to non-toxic products and procaine is also inactivated in the plasma by circulating cholinesterase. Local anaesthetics can be divided into two general groups: those detoxified rapidly (e.g. procaine) and those detoxified slowly (e.g. cocaine). From a practical stand point, the toxicity of a local anaesthetic is determined by the ratio between the rate of absorption and the rate of destruction.

Chemistry of local Anaesthetics

The very large numbers of local anaesthetics available have many actions in common and their chemical structural show many similarities. The very large numbers of local anaesthetics available have many actions in common and their chemical structural show many similarities. The very large number of local anaesthetics available has many actions in common and their chemical structural show many similarities. They are all water soluble salts of lipid-soluble alkaloids and consist basically of three parts, an amino group, a connecting group with which an ester or amiole, and an amino alcohol residue in which the amino group may be substituted by alkly groups or form part of an alicyclic ring. Alterations in all three parts of the molecule give compounds of varying potency and toxicity. Local anaesthetics may be divided into three main groups

1. Cocaine, a naturally occurring alkaloid and the first local anaesthetics to be used.
2. Para-aminobenzoic acid derivatives/(procaine, amethocaine etc)
3. Agents including lignocaine, cinchocaine, benzocaine many of which chemically resemble the AARA drugs.

The Administration of Local Anaesthetics

Local anaesthetics may be administered in a number of ways:

1. As a cream, ointment, spray, solution or powder to mucous membranes or to damaged skin around wounds.
2. By infiltration. The drugs may be injected locally into subcutaneous tissue to block sensation for the performance of minor superficial surgery.
3. By injection into the subarachnoid of space of the spinal cord to produce block of motor and sensory roots of and autonomic fibres. This is known as spinal anaesthesia and will block the sensation of pain from the regions of body innovated by the affected segments of the spinal cord.
4. By injection near a major nerve trunks to block sensation from the truncated region of the body e.g. brachial plexus block.

Potentiation of effects of L.A.

Effects of local anaesthetics may be potentiated by the use of vasoconstrictors such as adrenaline and by hyaluronidase. Addition of adrenaline HCL or other vasoconstrictors to a solution of the drug will prolong the action of local anaesthetics. Cocaines the only

exception it has a clearest vasoconstrictor effect. The sterile 1:1000 solution of adrenaline is added to a local anaesthetics solution following sterilization and shortly before use. A concentration of one part of adrenaline in 50,000 parts of L.A. solution should not be exceeded and in 1 in 100,000 is preferred. Vasoconstrictors also decrease the toxicity of a L.A. by delaying absorption and preventing high blood concentrations since slower absorption provides more fibre destruction of a local anaesthetics by the tissues of the body. Hyaluronidase, a mycolytic enzyme, hydrolyses by a hyaluronic acid and increases diffusion of injected substances. It may be added to local anaesthetics solutions to injected S.C. to promote tissue diffusion and thereby to increase the duration of anaesthesia may be due to extensive absorption of L.A. Hyaluronidase has two shortcomings:

1. It may enhance absorption and toxicity of L.A.
2. It is expensive and these two have its wide application in veterinary practice.

Local Anaesthetic Agents.

Procaine HCL – Procaine HCl is a white crystalline powder dissolving in an equal weight of water. Solutions of procaine HCl can be sterilized repeatedly by boiling w/o loss of anaesthetic potency but the boiling should not be done as metal vessels or glass that contain alkalis. A distinct should be discarded.

Pharmacological Action

Procaine was synthesized after cocaine was discovered to be habit forming and relatively toxic. Procaine HCl is the most widely used and the most satisfactory of all the LAs. A large number of LA compounds have been studied toxicity associated with an increased anaesthetic efficiency. Procaine is not as active as cocaine. However, it is considerably less toxic than cocaine and most other commonly used local anaesthetics. The solution of HCL is nonirritant and promptly effective when injected subcutaneously. Anaesthesia is relatively brief because the drug is absorbed rapidly and destroyed quickly by the liver. Anaesthesia with procaine is commonly prolonged by the addition of a vasoconstrictor to the solution to delay absorption of the local anesthetic from the site of injection.

Metabolism:

Procaine is hydrolyzed primarily in the liver and, tissues of the body. In the cat the liver is responsible for up to 40% of the procaine metabolism. An-enzyme hydrolyzes

procaine to PABA and diethyl aminoethanol. The enzyme procaine esterase is the same as plasma cholinesterase. The kidneys play no significant part in the reduction of procaine blood levels. But they excrete PABA rapidly and to a considerable extent. PABA exhibit no local anesthetic action Diethyl amino ethanol possesses only a part of the full anesthetic activity of procaine.

Toxicity

A rapid i.v injection of procaine (45mg/ kg) from the cat or rabbit produces a lethal effect; if the drug is administered slowly or by s.c route, the dose required to produced death as about 10 times greater. The greatest difference between the toxicities of procaine HCL and a potent local anesthetic such as cocaine HCL is the rate of metabolism. Cocaine is slowly metabolized whereas procaine is rapidly detoxified.

The use of procaine when the ambient temperature is high may lead to increased absorption from s.c infiltration sites to the extent that CNS stimulation or convulsions occur. Vasoconstrictor agents should be employed into the L.A to reduce or prevent this problem. If convulsions occur the use of the ultra short- acting barbiturates i.v. are indicated.

Clinical use.

Local anesthetic by tissue infiltration with a procaine HCL solution is a routine clinical technique employed for the relieve of pain The majority of these clinical applications are to relieve pain of the skin. Anaesthesia is produce by anaesthetizing a major nerve supply of specific areas, such as perineural injection of the mandibular nerve for a dental operation in the dog, of the cornual nerve for dehorning in the goat or cow and of the last thoracic and first two lumber nerves on the left side for rumenotomy or caesarean section in the cow. Procaine is also used to reduce or anaesthesia or anesthesia for tail docking in the lamb. Or dog, for nerve blocks in the foot and for enucleation of the surgical removal of the eye ball from its socket or shelling out of a tumour or origin from its capsule of the eye in cattle referred to as peterson eye block. In the recent years procaine has been used intravenously to produce retrograde regional anesthesia of the ruminants. In cattle, procaine is used epidurally to produce anesthesia for obstetrical procedures and perineal operations. The use in small animals has not been as frequent because of the problem with restraint of the animal during surgery.

Procaine hydrochloride is used as veterinary medicine for infiltration, conduction and epidural anaesthesia. For infiltration in small animals, a concentration of 1% is generally employed, whereas as larger animals 2% is preferable. About 2-5ml of a 2% solutions are used for nerve block or conduction anaesthesia in small animals. In large animals, 5-10ml of a 4% solutions are most commonly employed for this purpose. Adrenaline hydrochloride solution may be added to give a concentration of 1:100,000, i.e. 1ml of adrenaline HCL solution (1:1000) to each 99ml of anaesthetic solution.

For surface anaesthesia, procaine HCL is not as effective as other L.A. as it is rarely used.

I. V. Injection – In dogs and humans, i.v. injection of procaine HCL depresses cardiac irritability induced by general anaesthetic and thereby decreases the incidence of cardiac arrhythmias and ventricular fibrillation. This effect of procaine led to the development of procainamide HCL, which is used prophylactically and therapeutically for treatment of cardiac arrhythmias occurring in heart disease or from general anaesthesia/. I.V. procaine HCL has been used as a treatment of spasmodic colic in horses and is suited to this type (i.e. “spasmodic”) of colic.

Stimulant Action

The horse seems to be more sensitive to the CNS stimulation of procaine HCL than other species of domestic animals. Stimulation produced in the horse by procaine resemble that of opiate doping. Central stimulation of cow using procaine need a considerable larger dose, whereas, the pig falls intermediately between the horse and the cow. Dure to its CNS stimulant and analgesic actions, procaine has been used illegally in race animals to improve performance and/or to mask lamelessness in track and racing events.

LIGNOCAINE

Lignocaine (Lidocaine) as a white or slightly yellow powder with a characteristic odour, it is relatively stable but nearly insoluble in water.

Metabolism and fate:

Lignocaine is metabolized primarily in liver at a rate nearly as rapid as that of procaine. The unchanged form is excreted in the urine of the dog in a concentration of 10% - 20%. A large amount of lignocaine is conjugated with sulphate and excreted in this form. Following the i. v. administration of lignocaine (10mg/kg) in pregnant guinea pigs, it

rapidly crosses the placenta. High concentrations are found in the fetal liver, heart, and brain. The kinetics and oral absorption rate of lignocaine have been determined in the dog, 78% of the administered dose of lignocaine reaches the general circulation. Emesis occurs regularly at 2.5 hours after the administration of lignocaine.

Pharmacological Action:

Lignocaine HCL is a water soluble, local anaesthetic that produces more prompt, potent, and extensive anaesthesia than an equal concentration of procaine HCL. In fact, the anaesthetic potency and area of anaesthesia are about twice those of procaine HCL.

Lignocaine is used for infiltration, nerve conduction, epidermal topical anaesthesia. Depending on the concentration of solution and the procedure, the onset of mucosal anaesthesia appears in about 5 minutes and the effect persists for 30 minutes or more. Lignocaine HCL is effective at about one half of the concentration of procaine.

For infiltration anaesthesia, 0.5% is normally used in small animals of Adrenaline HCL. For conduction anaesthesia, a concentration of 1% in large animals and 2% -3% in large animals is used usually with a vasoconstrictor. In the horse, 50 and 30ml of a 2% solution are effective in blocking the thoracic and pelvic limbs respectively. A concentration of 1%-2% lignocaine HCL is suggested for epidermal injections.

Clinical Use

In dogs and cats: The epidural use of lignocaine HCL (1ml of a 2% solution per 4/5kg or 20mg/4.5kg) will block cranially to lumbar vertebra I (L₁) and 1ml of a 2% solution per 3.4kg will block to thoracic vertebrae 5 (T₅) in the average dog or cat. The onset of epidural analgesia with lignocaine is relatively rapid. 3-12 minutes and the duration of action is 45-90 minutes. In the treatment of cardiac arrhythmia, lidocaine is used intravenously at the rate of 2mg/kg every 20-30 minutes.

In pigs, Goats and Sheep: In the pig dosage of lidocaine required to produce epidural anaesthesia to T₁₀ to permit a laparotomy has been determined by the length (in cm) of the animal measured from the external occipital protuberance to the first coccygeal vertebrae. The recommended dose of 2% lignocaine up to 40cm in length is 1ml, after this an additional 1.5ml are administered for every 10cm increase in the vertebra column of the pig. The dose/length relationship also applies to the dog.

Lignocaine HCl (1% or 2%) has been used in corneal nerve block of the goat; 2ml of the L.A are injected at each site to block the lacrimal and infratrochlear branches of the corneal nerve. In adult sheep lignocaine (2%) has been used for epidural anesthesia. About 10 minutes prior to the epidural injection a phenothiazine tranquilizer such as chlorpromazine HCl (25-50mg) is admin. 1m . the dose of lignocaine varies from 8to 12ml: onset of anesthesia occurs 2-10 minutes after the injections. The analgesia produced by lignocaine in sheep it preceded by a short period of muscular twitching, which is followed by profound relaxation.

For use as spinal (intrathecal) anesthetic, a 2% lignocaine solution (5ml) is injected into the lombosacral space of sheep. Anesthesia last on average for more than on have.

In cattle: In cattle, lignocaine is preferred for a number of surgical procedures in conjunction with tranquilizers. For low epidural analgesia 4ml of a 2% solution has been used w/o & with 1:80,000 Adrenaline. In cattle where high epidural analgesia was produced, 60ml of a 2% lignocaine hydrochloride solution were used, this dose produced recumbency in all animals. Analgesia lasted 220-360 minutes. For anesthesia with lignocaine involving the lower portion of the limbs of cattle, a tourniquet is placed around the limb just below or above a hock. Then 10-20ml of 2% lignocaine hydrochloride are injected into any superficial vein below the tourniquet. Rapid anesthesia develops and normal sensation and limb movements return 5 minutes after release of the tourniquet.

In Horses: Lignocaine is probably the most commonly used local anesthetic for nerve blocks in the equine. 10 to 20 ml of 20% lignocaine blocks the mandibular nerve and desensitizes the mandible, lower molars, incisors and lower lips. Blockage of other major nerves usually does not require as great a volume of anesthetic

Toxicity: when injected w/o adrenaline sufficient lignocaine is absorbed from the site of a nerve block or regional anesthesia to depress the CNS, producing a general drowsiness. Local irritate is rare. Over dosage will cause muscular twitching, hypertension, nausea.

URINARY SYSTEM

DIURETIC DRUGS

Definition:- Diuretic drugs are drugs that induce a state of increased urine flow.

The reason for the knowledge of this group of drugs is paramount for the following reason

- A therapist or clinician should have a basic knowledge, due to the increased prevalence of urinary disorders in humans, and animals especially small animals.
- Distortion of body fluid volume could result due to a disease condition
- Distortion in equilibrium of acid-base composition or electrolytic composition
- Disorders or clinical problems of urinary origin are life threatening (problems involving the urinary system are life threatening and need immediate intervention.)

Indication of Diuretics

1. Oedema
2. Correction of specific ion imbalance
3. Reduction in the rate of intraocular fluid pressure
4. Ascites that occur due to heart failure, kidney, and liver diseases
5. Hypercalcaemia
6. Reduction of polyuria of diabetes insipidus

It is important to note:-That localized oedema, such as may occur in lymphatic or venous disorders, as in ulcerative lymphangitis, human elephantiasis could not be mobilized by diuretic therapy.

A simplified fluid and electrolytes dynamics in the nephron

- Functional unit of kidney is nephron
- It is comprised of five functional regions
- Proximal convoluted
- Descending duct
- Ascending duct
- Henles loop
- Collecting duct

Proximal convoluted;- filtration (ultra filtration) and

(i) Reabsorption (ii) partial reabsorption

Reabsorption (complete):- glucose amino acid

reabsorption partial(Na^+ , k^+ , and HCO_3^-)

the function of proximal tubule, loop of Henle are invariant and are freely permeable to water.

Distal Convoluted tubule:- Is subjected to regulation by *aldosterone*, aldosterone is a mineralcorticoid that stimulates Na^+ / K^+ ATPase pump that activates the expulsion of Na^+ from the tubular surrounding into the interstitial fluid

It is important to note that H^+ are exchange for Na^+ under the influence of carbonic anhydrase.

Some specific points to note.

- About 16-20% of the blood is plasma filtered from the glomerular capillaries into the Bowman's capsule by hydrostatic pressure at about 120ml/minute.
- 62 liters is filtered per day in dog.
- Osmolarity of dog urine may vary from 40-2500mOsm/kg of water.
- The glomerular filtrate is 15 osmotic with plasma (290-310mOsm/L of Water).

Classes of Diuretics

This include;

The loop diuretics

Thiazides

Potassium-sparing diuretics.

The diuretics no longer in use are the *organomercurials* and the *carbonic anhydrase inhibitors*.

Others are diuretics that are low in potency this include

- a. Methylxanthines
- b. Aminouracils
- c. Osmotic agents

Loop diuretics (high ceiling)

The loop diuretics are of highest efficacy in mobilizing Na^+ and Cl^- for this reason they are called the *high ceiling diuretic*

Chemical constituents or chemistry: they are carboxylic acids

Examples:-
Furosemide
Ethacrynic acid
Bumetanide
Muzolimine
Torsemide

Furosemide:- is chemically related to thiazides it is 8-10 times more potent

Ethacrynic acid is phenol oxyacetic acid derivative and was synthesized as a sulphydryl (-SH) enzyme blocker

Mode of action

To remember their mode of action remembers their class name loop. Thus, the loop diuretic inhibit Na^+ - K^+ Cl^- Co - transportation in the thick, ascending limb of “loop of Henle” so they decrease the reabsorption of Na^+ , K^+ and Cl^-

Pharmacokinetics of loop diuretic examples of these are furosemide

- After an intravenous injection
- The drug reaches its peak concentration in 30 minutes and persists for 3-6 hours
- Diuresis onset is 5 minutes after administration and persists for 24 hours.
- In oral administration, diuresis onset is 1 hour in simple-stomached animals its peak at 6-8 hours
- In cow up to 6 hours is required to obtain maximum effect in oral administration in cow.
- Furosemide is highly bound to plasma proteins. It is partially conjugated with *glucuronic acid* (20%) and is mainly excreted in urine.

Some points to note

- Bumetanide is 40-60 times more potent than furosemide., and is 100 times more potent when administered orally
- Ethacrynic acid is less potent than furosemide.

Therapeutic uses

- Required when there is need for repaid mobilization of oedema
- Cerebral oedema
- Udder oedema
- Hydrothrorax
- Ascites
- In race horses it is use to prevent exercise-induced pulmonary hemorrhages and epistaxis.

Adverse effect

Cats are more sensitive than dogs

- Fluid and electrolyte imbalances
- Hypokalaemia.
- It should not be administered with ototoxic drug (eg. Amino glycosides)

Dose - Students should find out

THIAZIDES

Chemistry:- Thiazides are heterocyclic compounds with benzene ring and an unsubstituted sulphonamide. Thiazides are the most widely used diuretics

Examples are:-

Chlorothiazide

Hydrochlorothiazide

Hydroflumethiazide

Cyclopentiazide

Trichlormethiazide

Benzthiazide

To remember the examples remember the suffix “*thiazide*”

The mode of action

Inhibition of sodium, chloride, and water.

Pharmacokinetics of thiazides

- When administered orally or parenterally they well absorbed.

- They become distributed throughout the extracellular space.
- They accumulate only in the tissue of the kidney.
- Their onset of action is one hour, their duration of action varies.
- Chlorothiazide – 6-12hours
- Bendrofliazide – 24hours
- Their drug life in 40hours.
- They are not metabolized but are excreted by active tubular secretion.

Renal effect of thiazides

- **Increased excretion of Na⁺ and Cl⁻.** This occurs from the distal tubule to decrease the reabsorption of Na⁺ by inhibition of Na⁺-Cl⁻ symport (means co-transportation of solute species in the same direction).
- **Loss of K⁺.** thiazides act proximal to the site of aldosterone-stimulated Na⁺ and K⁺ exchange.

The delivery of great amount of Na⁺ this, means greater exchange and loss of K⁺. In exchange therefore a prolonged usage of the drug might predispose to hypokalemia.

- **Decreased calcium excretion.** The thiazides decrease calcium re-absorption of Ca⁺⁺. They also decrease urinary uric acid excretion.

Reduced peripheral vascular resistance

There is a reduction in blood pressure resulting from decrease in blood volume. But this later normalizes to recovery, but prolonged usage might cause hypotensive effects.

Note:- For this reasons thiazides are given concomitantly with anti hypertensive drugs like *reserpine, hydralazine, nifedipine and veratrum*

Therapeutic uses

The least three members of the group are used chlorothizide, hydro-chlorothiazide, and bendrofluazide.

- **Oedematous states**

1. milder case of oedema.
2. parturient udder oedema in cows and goats
3. cardiac and nephritic oedema.
4. bowel oedema of pigs
5. post operative and non-specific oedema due to trauma.

- **Salt poisoning/pseudocyesis.**

Thiazides are indicated to hormonal therapy to inhibit lactation, especially in pseudocyesis.

- **Hypertension** have long been the mainstay of anti hypertensive medication in humans
- **Diabetes insipidus** (di):- thiazides have the unique ability to produce hyper osmolar urine. Paradoxically they have been used to treat di of renal origin

Read dose of various Thiazides used in vet-medicine

Potassium-sparing diuretics

Examples spironolactone, triamterene, and amiloride are weak diuretics when used alone, causing only 1-2 percent of filtered sodium load to be excreted.

They act in the distal tubule and oppose the potassium excretion promoted by aldosterone. They can thus help to ameliorate potassium loss caused by more potent diuretics. Hydrochlorothiazide and amiloride; are combined examples co-amiloride

Spironolactone

Spironolactone, a synthetic steroid lactone is a competitive antagonist of the mineralocorticoid aldosterone. It interferes with aldosterone-mediated Na^+ - K^+ exchange at the late. Distal tubule, increasing Na^+ loss while decreasing K^+ loss.

Pharmacokinetics

- Spironolactone is well absorbed orally, but undergoes entero-hepatic circulation.
- Its onset of action is slow, and effects occur within 48-72 hours.
- It is highly protein bound to plasma proteins but rapidly metabolized in the gut.

Uses of spironolactone

- It is indicated for treating oedema of congestive heart failure.
- Oedema resulting from primary hyperaldosteronism.
- It used as an adjunct to either thiazide or a loop diuretic to counter excessive K^+ loss.

Adverse effects of spironolactone.

- Hyperkalemia
- Gastrointestinal disturbances
- Spironolactone chemically resembles sex steroids. It has oestrogenic side-effects and may induce gynaecomastia.
- Impotence in males and menstrual irregularities in females.

TRIAMTERENE AND AMILORIDE

Mechanism of action

It inhibits active Na^+ reabsorption in the distal and collecting tubules, resulting in decrease in $Na^+ - K^+$ exchange, hence a decrease in K^+ loss.

Pharmacokinetics of Triamterene and amiloride

- It is well absorbed after oral administration.
- Its diuretic effect could be felt for 10 hours.
- Amiloride on the other hand is poorly absorbed orally only quarter of the oral dose is absorbed but it is 10 times more potent than triameterine.
- Amiloride is not bound to plasma protein and not metabolized. The maximum effect occurs about 6 hours after an oral dose, and the plasma half-life is 10-20 hours.

OSMOTIC DIURETICS

The osmotic diuretics are not much in use in veterinary practice.

- They are small molecular weight substances.
- The filtered by the glomerular but not, reabsorbed by the renal tubules, this increase osmolality of the tubular fluid. Because the proximal tubule and the descending loop are freely permeable to water.

Examples: *mannitol, urea, glycerol, isoserbide.*

They are therapeutically used

- In rapid reduction of intraocular pressure in glaucoma.
- To reduce the pressure and volume of cerebrospinal fluid and hence decrease in intracranial pressure in neuro surgery
- Mannitol could be administered
- It is not absorbed orally.
- It pharmacological inert and could be given in large quantity.

METHYLYXANTHINES

Examples; theophylline, theobromide, other examples caffeine.

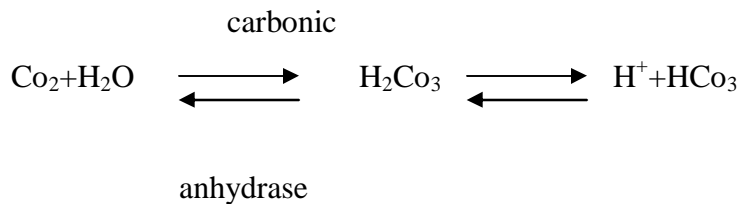
- The class of drugs has mild diuretic action due to the direct impact on the smooth muscle relaxation.
- Direct inhibitory effect on salt reabsorption in the proximal tubule.
- Theophylline is the most potent, but theobromine can be given in very large dose without producing cerebral stimulation; it is also irritating to the gut.

Amino uracils.

- They are related to the xanthines.
- They are synthesized.
- Example – aminometradine, dyphylline chlorazanil
- The potency of xanthines and amino uracils is much less than thiazides.

Carbonic anhydrous inhibitors

Carbonic anhydrase is present in the nephron sites, especially in the luminal membrane of the proximal tubule where it catalyses the reversal of carbon dioxide to carbonic acid, this is spontaneously ionizes to hydrogen and bicarbonate ions.



So, the carbonic anhydrase inhibitors inhibit these enzyme thus reduces the availability of H^+ generation is reduced.

HCO_3^- is lost in urine with marked elevation in urinary pH.

The loss of HCO_3^- causes hyperchloraemic metabolic acidosis and decreased diuretic efficacy following several days' therapy.

Examples are acetazolamide, methazolamide, ethazolamide.

Therapeutic uses

- Intraocular pressure of open angle glaucoma.
- It also decreases the production of aqueous humour probably by blocking the carbonic anhydrase pathway of the ciliary body of the eye.

Read doses and write doses of carbonic anhydrase inhibitors.

In comparison with thiazides and loop diuretics, carbonic anhydrase inhibitors are less efficacious.

URINARY TRACTS ANTISEPTICS

Urinary tract infections such as;

- Uncomplicated acute cystitis.
- Pyelonephritis.
- Urethral syndrome
- Prostatitis (these are acute infections).

Urinary tract antiseptics are totally synthetic and they exert anti-bacterial activity in urine.

They are 90% bound to plasma proteins.

The use of urinary antiseptics is in chronic urinary tract infections.

The infection of *E.coli*, other *coliforms streptococcus, proteus, pseudomonas* commonly used urinary tract antiseptics are nalidixic acid, oxolinic acid, fluoroquinolones e.g. profloxacin, enrofloxacin, norfloxacin, pefloxacin or lomefloxacin, enoxacin, fleroxacin, methenamine mandelate.

GASTRO INTESTINAL DRUGS

Drugs that exert useful effects on the Git modify mainly various mechanisms that control secretion and motility. Such drugs may be grouped as:

- Appetite Stimulants
- Sialogogues
- Anti Sialogogues
- Gastric stimulants
- Gastric Sedatives
- Ulcer-healing drugs
- Emetics
- Anti- emetics
- Laxatives
- Purgatives
- Ruminatorics
- Muscosal Protectants: (Carminatives, antizmotics astrigernts)

Appetite stimulants

- Feed intake is regulated by regulatory mechanism
- There is long-term and short-term regulatory mechanisms.

The long term mechanism regulates storage of nutrients in the body, while the short term regulates the appetite. The feed intake is regulated by the satiety center located in the ventromedial-hypothalamus. While the hunger center is the lateral hypothalamus. Inappetance or anorexia is common in disease states, manipulation may delay recovery and the animal may worsen.

Sialogogues

The loss of appetite that is often associated with disease can be treated by stimulating the taste buds on the tongue. There increasing the flow of saliva. These are termed sialogogues (or Sialics) older sialagogues are known as the bitters and are derived from plants derived compounds containing alkaloids e.g. gentian powder, ginger, capsicum, strychnine and brucine (from nux vomica) and quinine (from cinchona).

The drugs used as stimulants especially in monogastrics include B-complex, vitamins, glucocorticoids, anabolic steroids, benzodiazepines, cyproheptadine and zinc.

Glucocorticoids: Increase gluconeogenesis and antagonize insulin for an overall hyperglycaemic effect. The drug acts by stimulating the appetite of well being (euphoria) examples Prednisolone, dexamethasone. Continued use of glucocorticoid has catabolic effect; skeletal muscle and collagen protein are broken down to provide the precursor for gluconeogenesis other anabolic steroid associated with stimulation of appetite are stanozolol. Boldenone are synthetic derivatives of testosterone. Megestrol acetate a synthetic progestin also stimulates appetite especially in cancer patients and cachexia and could be used in dog and cats.

Benzodiazepines: (e.g. diazepam, oxazepam, elfazepam) are effective appetite stimulant in cats, cattle and sheep (but not dogs). The drug acts via the GABA activity by increasing GABA. Elfazepam is used in sheep and cattle.

Cyproheptadine: is an antihistamine with anti serotonin action, it promotes appetite by inhibiting 5-HT receptors which control satiety.

Zinc: is an essential for sensation of taste and the response of zinc supplements is often excellent, probably by suppression of satiety centre. Meat and meat extracts and provision of small amount of highly palatable, warm bland food e.g. (one part boiled or ground meat 4 part cooked rice) at frequent intervals could stimulate appetite in carnivores.

Dose of appetite stimulants

Prednisolone	1mg/kg P.O every other day
Stanozolol	0.25-3mg P.O once a day or 2-10mg/kg I.M, once weekly.
Diazepam	Cats: 0.05-0.4mg/kg I.M or I.v or 1mg/kg P.O once a day
Cyproheptadine	Cats: 1-4mg P.O, twice a day
Megestrol acetate	Dog: 5mg/kg P.O once a day
Dried yeast	Dog: Cats 8-15mg P.O once a day.

Appetite Suppressant

They are also called anorexiant, anorexigenic agents. They may be used as adjunct to proper diet and exercise.

Mechanism of action: They are stimulants of the cerebral hemispheres of the brain e.g. Pexotroamphetamine, Chlorphentermine

Indication: In obese animals.

Antisialagogues

Inhibition of salivary secretion is achieved by administering anti muscarinic drugs. Such as atropine, hyoscine (scopolamine), and hyoscyamine, which blocks cholinergic muscarinic receptors and decreases gastro intestinal motility and secretion others agent that reduce salivation are alum which will reduce it by astringent property. Kaolin would reduce saliva flow mechanically. These are not of any value in ruminants because secretion of considerable quantity of saliva is controlled by sympathetic nervous system and therefore muscarinic blockers are less effective in these animals.

Purgatives

The term laxative, aperient, cathartic, purgative and evacuant are synonymous. These are medicines that promote defecation largely by reducing the viscosity of the contents of the lower colon. They are classified as follows:

- Irritants (or stimulants)
- Stool bulking agents
- Osmotic laxatives and fecal softeners the (emollients).

Purgatives or Cathartics exert stronger action resulting in more fluid evacuation. These drugs in low doses act as laxatives and in higher doses acts as purgatives.

Indications

Clinically, laxatives are commonly used for relief of acute non dietary constipation or intestinal impaction.

- Removal of poisons from gut
- Prevent tenesmus in advanced Pregnancy or in Prolapse.
- Evacuation for surgery or radiography.
- To soften faeces after intestinal or anal surgery.
- Constipation or intestinal impaction
- Constipation

Irritant or stimulant laxatives

Vegetable oils, aloe, Senna, cascara, Sagraads, rheum.

Mechanism of action: Increasing water and electrolytic secretion by the gut mucosa and by increasing Peristalsis. This is done possible by the enteric nerves.

The vegetable oils (Castor, Linseed and olive oil) are hydrolysed by pancreatic lipases in the small intestine to irritating fatty acids (ricinoleic acid, linoleic acid and oleic acid) horses following ingestion of castor oil, mineral oil and vegetable oil such as cotton, seed oil, groundnut oil. Other examples include: Danthron, Phenolphthalein and bisacodyl

Bulk and osmotic laxatives

Stool bulking laxatives include Methylcellulose and certain plant gums for example agar-agar (a dried extract of Japanese sea weed) psyllium seed or (Plantain), Ispaghula husk, wheat bran and sterculia.

These agents are non starch Polysaccharide polymers from indigestible (in non ruminant parts of fruit and vegetables.

Wheat bran is perhaps the best known member of this group, it contains 40%, dietary fibre. Administration is at least for 2-3 days.

Indications

- Chronic constipation
- Used in dogs and cats when sharp foreign bodies have been swallowed needles, bones and stones. Simple dietary measures such as increased intake green vegetables fruits, tomatoes, puree, maize, guinea-corn, bran mash and whole meal bread is advised with handsome amount of water.

Dose

- Agar-Agar up to 10gm recommended in dose
- Ispaghula, by addition to feed.

Dog 5-15ml. 1-2 times daily

Cat 5ml, 1-2 times daily

Methylcellulose

Dog 0.5-5gm

Cat 0.5-1gm

Osmotic laxative

The osmotic laxative consist of non absorbable or poorly absorbed in organic salts or polymers that hold water in the intestine by osmosis and distends the bowel. They are cathartics of choice for elimination of poison. They increase peristalses and bring about purgation in 1hr.

Castor oil

This is one of the oldest Purgatives

Source: Seeds *Ricinus Communis* Castor bean. The oil is bland and non-irritating

Pharmacokinetics

When given orally it is hydrolysed to ricinoleic acid and glycerol. Ricinoleic acid is an active Cathartic; it is poorly absorbed with an onset of action of 2-6 hours.

It is not used in ruminants

Vegetable oil

A side product of vegetable oil is glycerol and has a mild stimulant effect on the rectum when administered as a suppository. In addition some of the oil that escapes hydrolysis acts as a stool lubricant. Passage of a soft oil stool generally occurs within 4-8 hours in small animals and 12-18 hours in Cascara Sagrada (Sared bark), oleo these contain glycoside that are hydrolysed in large intestine to yield irritant anthraquinones, also called emoclins. They stimulate smooth muscle and increase colonic motility. Senna obtained from pods of *Cassia- acutifolia* contains sennosides A and B

Pharmacokinetics

Anthraquinone laxatives essentially are Pro-drugs following oral administration pass to the colon where bacteria liberate the active anthrol form, which either acts locally or it's absorbed into circulation, excreted in bile to act on the small intestine thus they use 6-8 hrs to elicit their effect.

Indications

Used in acute constipation in small and large animals

Care must be taken in dams because if this is excreted in milk it may produce purgation in the young. The cathartics of choice are magnesium sulphate (Epsom salt). Magnesium hydroxide (milk of magnesia) and Sodium Sulphate (Glaubers salt).

Osmotic laxatives include sugars alcohols lactulose, glycerin, Sorbitol and Mannitol.

Magnesium Sulphate

The most used in animals and birds; it is isotonic in 3.5 percent solution orally.

Dose: 0.25-1gm/kg in horses, cattle, pigs and sheep.

Mg(OH)₂ as a 7-8.5 percent aqueous solution has a similar action to magnesium.

Horses	1-4l
Dog	5-10ml
Cat	2-6 ml

Sodium Salts

(Sulphate, Phosphate, Potassium tartrate) are also effective as saline laxatives. Sodium sulphate is the most effective saline bulk Cathartic on a molar basis. It has been used widely in horses as Carlsbad salt.

A mixture of 5 parts sodium sulphate, 2 parts sodium carbonate and 1 part sodium chloride. It is less toxic than magnesium Cathartics following absorption. Sodium Potassium tartarate (Rochelle salt) used as 5-7.5 percent solutions is relatively pleasant tasting.

Adverse effects

- Hypertonic solutions can produce significant dehydration, and must therefore, be administered with sufficient water to avoid this.
- Mg²⁺ Predispose to toxicity in patients with congestive heart failure or renal disease.
- Phosphate laxative can cause hyper phosphataemia and reduction of calcium ion

Faecal softeners (emollient)

Surface active agents that become emulsified with stool serve to hydrate and soften it and make passage easier example mineral oil, glycerin, anionic detergent, (dicotyl sodium, sulpho succinate) also called decussate sodium.

Dose of Decussate Sodium.

Cattle horses	5-15 gm
Dog, cat	15-30mg

Neuromuscular cathartics

Drugs that stimulate muscarinic receptors (e.g. arecoline, carbachol, bethanecol) or inhibit Cholinesterase (e.g. neostigmine). Increase smooth muscle activity in the gastro intestinal tract. Carbachol is a potent gastro intestinal stimulant and as such be dangerous in cases of intestinal obstruction, where rupture or intestinal intus susception can occur. Bathanecol is preferable Arecoline has been used both as a purgative and as an anthelmintic (taenicide) where intestinal stimulation assists in expelling worms. In horses is given at (dose rate of 140mg) and cattle (dose 4-33mg) The anti-cholinesterase, neostigmine has mild gastrointestinal stimulant used to treat ruminal stasis, impaction. At any urinary tract obstruction.

Dose of neostigmine

4-25mg Dog

0.25-2.5mg Cat

Anti-diarrhoeal drugs

Diarrhoea is the frequent passage of liquid stools. There are numerous causes including infectious agents, toxins, anxiety, drugs, e.t.c it involves increased Git motility, increased in secretion and a decrease in adsorption of fluid and thus a loss of electrolytes (Particularly Na⁺) and water

Classes of anti diarrhoea drugs

- Motility modifiers
- Intestinal protectant
- Adsorbent and drug that modify fluid and electrolyte transport additional to these.
- Anti microbials
- Anti inflammatory drugs
- Anti parasitic and anti toxins

Anti motility drugs

Anti – cholinergic drugs(e.g atropine, hyoscine and benzetimide) inhibit propulsive and non propulsive gastro intestinal motility. Hyoscine is utilized with an analgesic dipyrone In a parenteral formulation that appears useful in the treatment of acute intestinal spasm. To avoid C.N.S excitement, the parasym patholytic quaternary amines such aminopentamide is opropamide, methantheline, propantheline and oxyphenonium are

preferred because they do not cross the BBB readily. They inhibit normal cholinergically mediated basal secretion of the gastro intestinal tract.

Opiates

They increase smooth muscle tone and decrease peristalsis and inhibit acetylcholine release. In addition opiates directly stimulate absorption of fluid and electrolytes via U-Opiate receptors in the intestinal mucosa and C.N.S. They also have anti secretory effect. The constipating effect of morphine and codeine preclude their clinical use as anti diarrhoeal drugs. Camphorated tincture of opium (Paregoric). Oral dose rate of 1-3ml, 2-3 times a day in dogs and cats and 4-6ml/100kg of body weight, once daily in calves and foals.

Other examples of synthetic opiates Diphenoxylate, Loperamide,

Agents that modify fluid and electrolyte transport

- Non steroidal anti – inflammatory agents such as aspirin and indomethacin are effective in controlling diarrhea. Their anti diarrhoeal action is probably due to inhibition of prostaglandin synthesis. Bismuth subsalicylate is considered to be an anti –diarrhoeal.

Indication

- Acute diarrhea
- Enterotoxigenic
- *E. Coli*
- Traveler's diarrhea

Fluid replacement

Dehydration and electrolyte loss are the major causes of death in severely affected diarrhoeic young animals.

ORT(oral rehydration therapy) constitutes the following

Glucose (10.75gm/litre) or amino acid e.g. (glycine 4.5gm/l) or both these solutions contain sodium chloride, (3.5gm/l) Potassium chloride, (1gm/l) and sodium bicarbonate.

Mechanism: enhances absorption electrolytes by the enterocyte continues during diarrhea and thus helps in replacement of water and electrolyte loss.

Adsorbent and protectant

Adsorbent agents include kaolin, (magnesium, aluminum silicate) activated attapulgitte (derived from wood peat, coconut or pecan shells) and pectin (carbohydrate polymer extracted from the rind of citrus fruits) are inert substances that are popular for symptomatic therapy of acute diarrhea. These agents adsorb enterotoxins or microorganisms and provide a protective coating on inflamed intestinal mucosa. Kaolin-pectin is administered to animals foal, calves, swine, birds, lamb and kids every 4-6 hours.

Astringents

Astringents cause local precipitation of proteins on skin or mucosa membrane which provide a protective barrier for the tissue beneath. They do not penetrate cells, thus affecting the superficial layer only. Zinc, aluminum and zirconium salts have astringent actions but their use is limited to external surfaces. Intestinal astringents are tannic acid and tannins found in many plants. Tannic acid is generally obtained from nut galls, oak and tannins are found in tea, catechu, nutmeg, areca, betel (nut). They denature proteins forming protein tannate which coats and averts the bowel mucosa.

Anti microbial agents and diarrhoeal therapy

Frequently, the need arises to turn to the chemotherapy of pathogenic enteric microorganisms, protozoa, and bacteria, anti microbial agents that are usually combined with one or more of the anti diarrhoeal preparations discussed above. For example Biosol M is a combination of neomycin and methscopolamine useful in the treatment of bacterial enteric disease. Other anti microbial agents used are

- Oxytetracycline, amoxicillin,

Clavulanate-potentiated amoxicillin and trimethoprim is potentiated sulphonamides. Oxolinic acid, nalidixic acid is reported to be a potentially promising drug for treatment of neonatal calf diarrhea.

Metronidazole, a nitroimidazole, an anti protozoal, are used to treat chronic inflammatory bowel disease and colitis in dogs and cats.

Emetics

- Peripherally acting emetic
- Zinc sulphate
- Copper sulphate

- Sodium carbonate
- Ipcac

Induce emesis reflexly by stimulating sympathetic and vegal afferent receptors (i.e. sensitivity nerves endings) Pharynx and stomach mucosa.

Central Apomordine 0.07mg/kg acting morphine xylazine.

Antiemetics

- Antiemetics are drugs used to prevent or suppress excessive vomiting.
- Used in treating motive sickness
- Chronic gastritis
- Control of emesis from radiation and chemotherapy.
- Labyrinthine disease

Classes of anti-emetics

- Demulcents
- Local gastric sedatives and central antiemetics

Demulcents

Sooth inflammed or denuded mucosa or skin.

Molecular weight: High Molecular weight substances and are applied as thick colloidal or viscid e.g. gum acacia, gum toragacnath, glycerine, methyl cellulose, propylene, glycol.

Local gastric sedatives:

These are local nerve sedatives and they are protectants pectin, kaolin, local nerve sedatives atropine, hyoscine butacaine, tetracaine.

Central antiemetics

The major categories of drugs used to control nausea and vomiting: dopamine D₂ receptor antagonists (e.g. phenothiazines substituted benamides butyrophenones, 5-HT₃ serotonin receptor antagonists.

Histamine receptor antagonist – antimuscarinic; corticosteroids; cannabinoids and benzodiazepines.

Phenothiazines – acepromatzine; chlorpromazine, prochlorerazine and promazine.

Substituted benzamides e.g. metoclopramide, Trimethpobenzamine and Butyrophenones e.g. haloperidol droperidol.

Antihistamines e.g. Diphenhydramine, meclizine, cyclizine, promethazine and cinnarizine.

Diphenidol – indicated for labyrinthitis this causes hallucination in human is a derivative of diphenylmethane.

Antimuscarinics – Aminopentamide, propanthelene, isopropamide, darbazine.

Combination regimens – Antiemetic drug are often combined to increase their activity or decrease toxicity.

- Dexamethazone is combined an 5-HT₃ antagonist namely *Ondasetron*
- High dose of metochopramide induce diarrhea so combined with diphenhydramine to reduce extrapyramidal effect.

Carminatives - They are drugs that aid errection (expulsion of gas from stomach indicated in ruminal typheni apart from trochar and cannula. Examples – Sodium bicarbonate, powder ginger, essential oils eucalyptus, pine, peppermint. They are used in flavouring of drugs. They bring about volatile oils by their mild irritant facility thus oesophageal sphincter and gastro-intestinal motility.

Anti-frothing Agent - They are cause defoaming agents increase surface tension of liquids. Thus reduce foam stability, e.g. oil of turpentine, liquid paraffin (kerosene), silicone polymere, dimethicone, poloxalene.

Oil of turpentine	-	30ml – 60ml
Li. Seed oil	-	300ml
Oil turpentine	-	30-60ml
Sheep	-	12-15ml
Swine	-	4ml
Cattle	-	4ml in 300ml
Sheep	-	0.6-1ml in 100ml water

Dimethicone

Cattle	-	100ml emulsion
Sheep	-	25mg/ml

Poloxalene	-	25ml emulsion
Cattle	-	22-44mg/kg P. O.

NEURO PHARMACOLOGY

Neurochemical Basis Of Depression

To remain behaviourally balanced there should be a balance between central monoamine containing and acetylcholine containing nerves. The central neuro-monoamine are serotonin, norepinephrine, and dopamine these are neurotransmitters.

If there is impairment in the serotonin and norepinephrine neurons overactive secretion of acetylcholine and thus decrease in the central monoamine containing.

So basically antidepressants act via:

- i. The increase of production of serotonin, norepinephrine and dopamine.
- ii. They also act via reduction of production of acetylcholine thus having anticholinergic effect.

Drugs Acting on C.N.S. To Cause Modification of Animal Behaviour

The cellular mechanisms of abnormal behaviour in humans or animals are yet to be fully known.

The most likely neurotransmitters (NTS) associated with abnormal behaviours can be identified based on the NTS targeted by drugs. These are:

- Biogenic amines serotonin
- Histamine (H₁ sub type)
- Monoamine dopamine
- The catecholamine norepinephrine
- Acetylcholine
- GABA, α -aminobutyric acid
- Excitatory amino acids.

Anti-Depressants

Tricyclic Anti-depressants

Examples – Clomipramine

Amintriptyline

Doxepin

The above named drugs are derivatives of imipramine currently clomipramine is the only one of these drugs that is approved.

Mechanism of Action

- Imipramine and its derivatives with a tertiary amine side chain block norepinephrine re-uptake is characterized by little effect on dopamine re-uptake.
- Clomipramine has marked effect on serotonin re-uptake.
- Doxepin has greater antihistaminergic.

Pharmacologic Effect:

On the Autonomic N.S.

The TCAS mood of pharmacologic effect reflects on the inhibition of norepinephrine. Antagonism of muscarinic cholinergic and α -adrenergic responses to N.T.S.

CVs

- Overdoses is life threatening
- Postural hypotension occurs due to blockage of α -adrenergic blockade.
- T.C.A. directly suppresses the myocardium.

Clinical Pharmacology of TCAS Anti-depressants

- They are very lipophilic and are absorbed well after oral administration.
- The drug is highly protein bound and the unbound drug would increase the volume distribution of the drug.
- The drug is eliminated by hepatic (oxidative) metabolism.
- Clomipramine is a drug of choice the dog anxiety

- Following the administration of clomipramine, the active metabolite was demethyl clomipramine, this accumulate following the repetitive of clomipramine.

Side Effects:

1. Cardiac toxicity
2. Dry mouth
3. Gastric distress
4. Constipation
5. Dizziness
6. Tachycardic
7. Arrhythmias
8. Blurred vision
9. Prosthetic hypertrophy

Indications

- Most abnormal behaviors amongst dogs and cats.
- These include fear, aggression, obsessive compulsive or self-mutilation disorders and excessive barking.

Contra-indications

- Metabolic diseases
- Cardiac and hepatic diseases
- Seizures
- Glaucoma
- Hyperthyroidism

Drug Interactions

The T.CAs can interact with a number of other drugs that compete for protein-binding sites with other highly protein-bound drugs. This cause impact on drug metabolism such as inhibition, induction of impact the clearance of the drugs.

- TCAs potentiate effects of sedative.

- Clomipramine inhibit the metabolism of other drugs.

Clinical use of TCAS

Most drugs take 2 to 3 weeks for clinical efficacy to be realized.

Amitriptyline is an exception, it elicit its effect in 3-5 days.

- Clomipramine elicits within 1-2 weeks.
- Monitoring is important to avoid toxicity.
- There is a risk of withdrawal due to physical dependence discontinuation should take over a week or if therapy is prolonged.

Selective serotonin Re-uptake

Inhibitors SSRIs

Drugs currently used are:

- Floxetine
- Paroxetine
- Sertraline
- Fluvoxamine

Mechanism of Action

SSRIs enhance CNS serotonin by blocking presynaptic neuronal uptake. They also increase postsynaptic receptor sensitivity.

Clinical Pharmacology

- Absorption of drug due to lipophilicity, protein-bounding and volume of distribution.
- Fluoxetine is metabolized by the liver to an active metabolite norfluoxetine and active metabolites.
- The active metabolites are long acting and interfere with the metabolism of other tricyclic antidepressants to bring about prolongation of their effect.
- Plasma concentration of fluoxetine is 100 to 300mg/ml
- While the plasma concentration of Paroxetine and Sertraline are 30 + 100 and 25 to 50mg/ml

Drug Interaction

- The S.S.RI can limit the metabolism of other drugs; the order of potency of inhibition is Proxetine > nor fluoxetine > fluoxetine = Sertraline
- Because of the risk of drug interaction this drug should not be combined with other anti depressants.

Side effects

- Gastro intestinal side effect
- Fluoxetine used for the treatment of lick granuloma caused
- Lethergy
- Hyperactivity
- Polydypsia
- Diarrhea
- Increased and decreased appetite

Clinical indication of selective Serotine reuptake inhibitors

- Fluoxetine was used for the following disorders
- Lick granuloma in dogs
- Separation anxiety
- Tail mutilation
- Psychogenic alopecia in cats
- Dominance aggression

Monoamine oxidase inhibitors

Example: Selegiline, Paragylene, Iproniazid

Mechanism of action

They affect the mono amino oxidase (MAO) inhibitors affect variety of monoamine by inhibiting Mitochondrial MAO and subsequent degradation of monoamines. Most notably dopamine. They elevate the mood of the depressed patient by inhibiting monoamine oxidase (MAO) enzyme

Pharmacologic effects

- Selegiline potentiates dopamine in selected neurons and has been approved to parkinsons disease in humans.

- Selegiline also scavenges oxygen radicals and reduces neurons damage due to reactive products of oxidative metabolism of dopamine or other compounds.

Clinical Pharmacology

- Readily absorbed after oral administration
- Maximal inhibition occurs within 5 to 10 days.

Side effects

- Hypertensive crisis: when aged cheeses containing tyramine (a bacterial monoamine-by product) when these are ingested in the presence of non selective MAO inhibitors.

Drug interaction

- Meparidine and precursors of biogenic amines.

MAO inhibitors relatively safe, but when combined with other anti depressants particularly those with the inhibition of the reuptake of serotonin.

Anti Psychotics

Psychotics are disorders in humans and animals that cause sever disturbance of the brain function that in characterized by thought and speech disruption and hallucination or delusion in veterinary practice these cases are rare but behavioural changes such as aggression, barking e.t.c. may occur.

Low Potency agents

- Acepromazine Chlorprazine and thoridazine hydrochloride.

High Potency agents

- Haloperidol
- Fluphenazine
- Trifluoperazine hydrochloride
- Prochlorperazine
- Thiothixene.
- Thiothixene
- Risperidone.

The Antipsychotia agents are also called neuroleptics.

Classification

1. Phenothiazines

- a. Aliphatic compounds
E.g. Chlorpromazine, Promazine, Promethazine.
- b. Piperidine derivatives: e.g. thioridazine.
- c. Piperazine compounds e.g. Prochlorperazine, Trifluoperazine, fluphenazine.

2. Butyrophenones.

Haloperidol, droperidol

3. Thiozanthenes

e.g. Thiothixene

4. Benzodiazepines

e.g. Clonazepam and others

Mechanism of action

i. Dopamine receptors blocking activity in brain. The receptors are identified by D1-D5 all are blocked these are present in the Mesolimbic system of the brain.

Neuroleptics or antischizophrenic or anti-psychotics also block the cholinergic, adrenergic and histamine receptors.

ii. Serotonin receptors – blocking activity in the brain.

The newer drugs block the serotonin and dopamine receptors of the brain.

Chlorpromazine (Largactil)

It is the prototype neuroleptic

Pharmacologic effect/ action.

C.N.S

- Blocks D1 to D5 receptors
- It does not depress intellectual function of patient
- It depresses the chemoreceptor trigger zone hence is used as antiemetic drug
- It potentiates analgesics and hypnotic effect.
- It blocks alpha adrenergic blocking and by inhibiting shivering it causes Hypothermic effect.

C.V.S

- It produces hypotension due to depress vasomotor center, vasodilation and cardiac depression
- It antagonism of adrenaline, acetylcholine histamine and serotonin.

Peripheral nerves

The drug has a potent local anesthetic action therefore used as antipruritus.

Endocrine system

This increases libido in females and decrease sex drive in males

Indication

1. Psychosis or mania
2. Vomiting
3. Hiccough.
4. Antipruritic agent to relieve itching
5. Used with narcotics to treat chronic pain

Side effect of the drug

a. CNS (effect)

- Parkinsonism
- Drowsiness and confusion
- Aggravate epilepsy
- Neuroleptic malignant syndrome

b. ANS (Autonomic Nervous System effect)

Anti cholinergic effect such as

- Drug mouth
- Urinary retention
- Loss of accommodation
- Constipation

Endocrine

- Infertility due to depressed hypothalamus

Hypersensitivity reactions

- Cholestatic jaundice
- Purplish discoloration of the skin.

- Hypersensitivity dermatitis
- Photosensitization
- Bone marrow depression.

Contraindication

1. Hepatic disease
2. Glaucoma
3. Urinary difficulty
4. Not used in horses
5. Contra indication in organophosphate poisoning
6. Contra indicated in epidural anesthesia

Promethazine (Phenergen)

It is similar to chlorpromazine but has marked antihistaminic and hypnotic action than chlorpromazine.

- Thioridazine is similar to chlorpromazine in action and side effects.
- Trifluoperazine is used as powerful antiemetic and tranquilizer.

Haloperidol

It is similar to chlorpromazine pharmacologically but is more potent dopamine antagonist, less potent & receptor blocker and weak anticholinergic is also act as an antiemetic. It has high incidence of developing extrapyramidal effects (Parkinsonism). It has also sedative effect than Chlorpromazine and has very low hypertensive effect.

Lithium. L

L is also called antimanic and mood stabilizing drug because it prevents mood swing in manic disorders

Mode of action

- It increases presynaptic destruction of catecholamines
- It inhibits release of transmitter at the synapse and decreases the sensitivity of the receptor

Side effects

Tremor, Ataxia, Anorexia, Weakness, Nephrogenic, Diabetes insipidus and thyroid enlargement.

The use of anti-psychotics in animals

It is used in dogs and cats

Administered with morphine and reduces the oxidation response caused by morphine in cats.

Breeding animals

1. Recommended in excitable sows following farrowing especially in those that are reluctant to accept their new borns.
2. For normal farrowing prior to farrowing
3. It is given in smoke to protect against heart stress
4. Useful as an adjunct treatment of agalactia which is a problem following parturition.
5. Used for restraint of wild life.

Dosing :

Dog 0.5 – 3mg/1b

Single 0.5mg/1b

Metabolism: of chlorpromazine is by glucuronide and sulfoxide conjugation and are excreted a sulfoxide.

CLASSIFICATION OF NARCOTIC ANALGESICS

1. Natural opium alkaloids :
 - Morphine
 - Codeine
2. Synthetic derivatives of opiates
 - Dihydromorphine (Dilaudid)
 - Herion (Diacetylmorphine)
3. Synthetic opiate-like drugs
 - Phenazince (Prinadol)
 - Meperidine (Demerol)

Narcotic antagonists

- Nalorphine (Alline)
- \Naloxene hydrochloride (Narcan)
- Diprenorphine

CHEMISTRY

Morphine is an alkaloid obtained from opium, which is the dried juice of the unripe seed capsules of the poppy plant.

Papaver somniferum, indigenous to Asia Minor. The opium contains two alkaloids namely Phenanthrene alkaloids and the benzylisoquinoline derivatives. The analgesic activity appears to depend upon 7-Phenyl-N-methylpiperidine groupings meperidine derivatives and the methadone compounds assume this structure. The two hydroxyl groups, one phenolic and the other alcoholic, are of great importance. Some of the natural morphine derivatives are obtained by simple modification on one or both of these groups. The morphine antagonist is prepared by replacement of the CH₃ group on the nitrogen by the alkyl radical – CH₂CH=CH₂.

PHARMACOLOGICAL ACTION OF MORPHINE EFFECTS

CNS – Analgesic – Morphine relieves practically all forms of pain, but is more effective against dull, constant pain than against sharp episodes of pain. Morphine relieves pain by increasing the pain threshold (intensify the pain) and by altering reaction to pain, causing a state of euphoria and sedation (the pain is there but the individual bears the pain better),

Respiration – Acts centrally to stimulate respiration which is followed by depression.

Vomition – It acts as both emetic and anti-emetic. It causes nausea and vomition initially. Vomition following morphine administration only occurs in dog and cat which are the only species that respond to central acting emetics like morphine and apomorphine.

Cough Reflex – It depresses cough reflexes. Here codeine is preferred to prevent respiratory depression.

Pupil (eye) – It causes pupillary constriction in man and dogs while in animals in which morphine is excitatory e.g. cat, swine, goats, sheep, cattle and horses it produces pupillary dilation (Mydriasis). In the bird, the pupil is not affected because of non-responsive skeletal muscles.

Spinal Cord – Morphine although depresses the CNS, it stimulates the spinal cord. Therefore, morphine is strictly contra-indicated in strychnine poisoning.

Cardiovascular system – Morphine increases ventricular function in man and dog. This is due to the increased level of circulating catecholamines. Hypotension occurs following

morphine administration. This occurs as a result of histamine release and depression of the vasomotor center. The cardiovascular function is un-important when morphine is given therapeutic dosages. This is fortunate as the drug may be used to relieve pains of myocardial infarction and in management of pulmonary edema of cardiac origin.

THERMOREGULATOR CENTER

Located in the hypothalamus is altered by morphine to the degree that generally lower body temperature. The dog administered morphine shows signs of panting which later stops when body temperature is lowered. The cat responds similar to dogs, but at higher doses, hyperthermia occurs and is maintained until morphine is completely metabolized. In horses, following morphine administration, sweating and hyperglycemia occurs as a result of increased circulating levels of epinephrine. In rabbits there is hyperthermia which may be related to increased level of circulating catecholamines.

GIT

Morphine increases the tone of the GIT smooth muscles and decreases motility of the GIT. It also decreases hydrochloric acid secretion and delays the passage of gastric content. The biliary and pancreatic secretions are diminished, delaying digestion in the small intestine. It also decreases the propulsive peristaltic waves in the small intestine and colon. It produces insensitivity to normal sensory stimuli for the defecation reflex due to central action. Causes constipation.

SPECIES VARIATION

Dog: Brief period of central excitement marked by restlessness, panting, salivation, nausea, vomiting, urination and defecation. This is then followed by depression.

Cat: Morphine causes excessive CNS stimulation in the cat. This excitation is thought to be due to the release of dopamine and norepinephrine in the brain. Drugs that deplete norepinephrine (reserpine, tetrabenazine) and those that block dopamine receptors (Chlorpromazine, haloperidol) in the brain can prevent this excitation.

Horse: Cattle, Goats, Swine, Ass are all excited by morphine. The mechanism is probably similar to what occurs in the cat.

ABSORPTION, FATE AND EXCRETION

Morphine is absorbed rapidly from the small intestine and after injection. The major pathway for biotransformation is conjugation with glucuronic acid, then excreted by the

kidney. The cat is deficient in this conjugation pathway lacking glucuronyl transferase enzyme. Hence, the half life of morphine is longer in cat.

Morphine is distributed in the kidney, liver, spleen and lung.

Contraindications

- Acutely, uronic and toxemic patients.
- Strychnine poisoning
- Tetanus
- Epileptic patients.
- Cardiovascular check.
- Hypotensive patients.
- Acutely Asthmatic patients

MORPHINE DERIVATIVES

Codeine (Methylmorphine) – is an important analgesic and antitussive drug. Used to allay irritating coughs in dogs. In therapeutic doses, it is less sedative an analgesic than morphine, but tolerance to the drug develops slowly and codeine is less addictive than morphine. It has less effect on the GIT and urinary tracts and on the pupil and causes less nausea and constipation than morphine. Codeine administered orally is not as effective an analgesic as when it is injected subcutaneously. Codeine is partly demethylated to morphine in the body and is partly changed to norcodeine. The conjugated forms of these compounds are excreted in the urine.

Dihydromorphine (Dilaudid) – is 5 times more potent than morphine in causing analgesia. Has a greater respiratory depressant effect than morphine, although it may be less nauseating and constipation has been used in dogs and cats.

Etorphine Hydrochloride (M-99) – is 10,000 times as potent as morphine as an analgesic. Used mainly in wild and exotic animals.

Oxymorphine HCL (Numorphan) – is 10 times more potent than morphine as an analgesic has been used in dogs and cats.

Morphine Substitute

Meperidine HCL (pethidine, demerol, dolantin). This is a non-morphine derivative. It has spasmolytic, analgesic and sedative activity.

Administration

I.M. is the best route for administration. Local irritation and pain result from subcutaneous route. In cat, irritation and salivation occur when meperidine contacts buccal mucosa, and following I.M. and S. C. administration in cat emesis does not occur, but defecation occurs in some animals. Oral administration is not advised in large animals because of cost.

METABOLISM AND FATE

Meperidine is absorbed following S.C., I.M., or oral administration. It has short duration of action (2 hours). It is inactivated in the liver by demethylation, though small amount is excreted unchanged in the urine.

PHARMACOLOGICAL EFFECTS

Thermoregulatory center – it produces hypothermia response following S. C. injection. This response may be related to the stimulation of dopamine receptor in the brain.

Cardiopulmonary effect – it slows down the heart rate and causes a fall in blood pressure in dogs following I.M. injection. Intravenous doses of 0.05mg/kg produce broncho-constriction. At 2.5mg/kg, lung capacity decrease by 22%. The above response is probably due to a central vagal effect and the release of histamine.

Analgesic Effect – Its analgesic action is between morphine and codeine. In dogs, cough reflexes is depressed satisfactorily.

Spasmolytic action or Effect on GIT – it spasmolytic action is less than that of morphine. Meperidine relax, the intestine, the bronchi, the ureter and the uterus slightly. Meperidine has the advantage over morphine in that it can produce analgesia before inhibiting the body, including the placental and fetal tissues, and is used to allay parturition pains in women because it does not depress fetal respiration.

Toxicity

It causes excitement and convulsing in cats when given subcutaneously in excess of 10-15mg per pound. This convulsion can be controlled by barbiturate administration. Meperidine potentiates the depressant effect of the barbiturates upon respiration. Nalophine is an antagonist of the respiratory depressant and toxic effects of meperidine. Because meperidine is rapidly metabolized in cumulative toxicity is observed, but doses up to 6 times therapeutic dose causes anorexia and weight loss.

Clinical Uses.

- Relieves pain
- Proanaesthetic medication.
- It can be used for the treatment of equine colic especially acute spasmodic condition.
- In cattle, it is used for calving to calm the nervous heifer and to provide analgesia during parturition.

Methadone (Dolophine)

This synthetic substance that has many of the properties of morphine including addiction in man. It is a good analgesic but produces respiratory depression. It is used in the relief of pain, treatment of narcotic abstinence syndrome and treatment of heroine users.

Phentanyl (R-4263; Fentanyl) – This is an analgesic agent whose potency is about 100 times more than that of morphine and 1000 times more than that of pethidine. It has been used to produce complete surgical anaesthesia in dogs but is usually given with a neuroleptic in neuroleptanalgesia. Fentanyl reduces sensitivity to pain in all animals and causes respiratory depression which can be counteracted with nalorphine. In dogs, rats and primates it induces sedation and myosis but in horses, mice and cats it is said to produce excitement and mydriasis. Phentanyl mixed with neuroleptics have certain advantages:

- Case of administration
- Wide safety margin
- Quite post-operative recovery
- Easily reversible with narcotic antagonists
- Well tolerated by patients or animals in poor physical condition.

Narcotic Antagonist

In veterinary practice, the ones of relevance are:

- Nalorphine
- Naloxone
- Diprenorhine

They are called opioid antagonist. They block effect of opiate receptors displacing narcotic molecules already present.

It is a morphine derivative.

Administration

S.C., I.M. or I.V.

Absorption and Fate:

It is readily absorbed fully by GIT and metabolism of naloxone is by conjugation of the liver.

Action

In the presence of narcotics, it has antagonistic effect.

- In the absence of morphine, it has C.N.S. depressant and analgesia.
- It does not antagonize mild respiration depressant.
- It does not cause constipation.
- It is a drug of choice for fetal respiratory depression of morphine in pregnant is antagonized without any effect on uterine motility, labour or incidence of still birth.
- It has typical withdrawal symptom in morphine addictive subjects.

Effect on Morphine Toxicity

1. Counteract sedation and respiratory depression of morphine which usually cause restlessness is counteracted after administration of Naloxone.
2. If first dose of Naloxone fails additional dosages is contra-indicated.
3. Over doses of Naloxone is treated by supporting respiration.

Dosage is 1mg for every 10mg of morphine or 20 mg of meperidine.

10 – 20mg to 1mg of etorphine.

Naloxone HCL

- It has potency for 10-30 times that of nalorphine.
- It does not produce respiratory depression which occurs with other narcotic antagonists.

Action

- It antagonizes respiratory depression caused by morphine, meperidine, oxymorphone.
- It does not antagonize the effect of inhalant anaesthetics, barbiturates, procaine or tranquilizers.
- The drug would also reverse the narcotic effect of fentanyl.

Administration

It could be administered by all parental routes however I.V. route is preferred for immediate effect.

Dosage

For reversal of respiratory depressant effect of narcotic in dog these dosages are recommended. 0.1mg of naloxone for 1.5mg of oxymorphone 0.016 – 0.1mg of naloxone for 0.02 – 0.03mg fentanyl. 0.016 – 0.1mg of naloxone for 0.5mg of morphine.

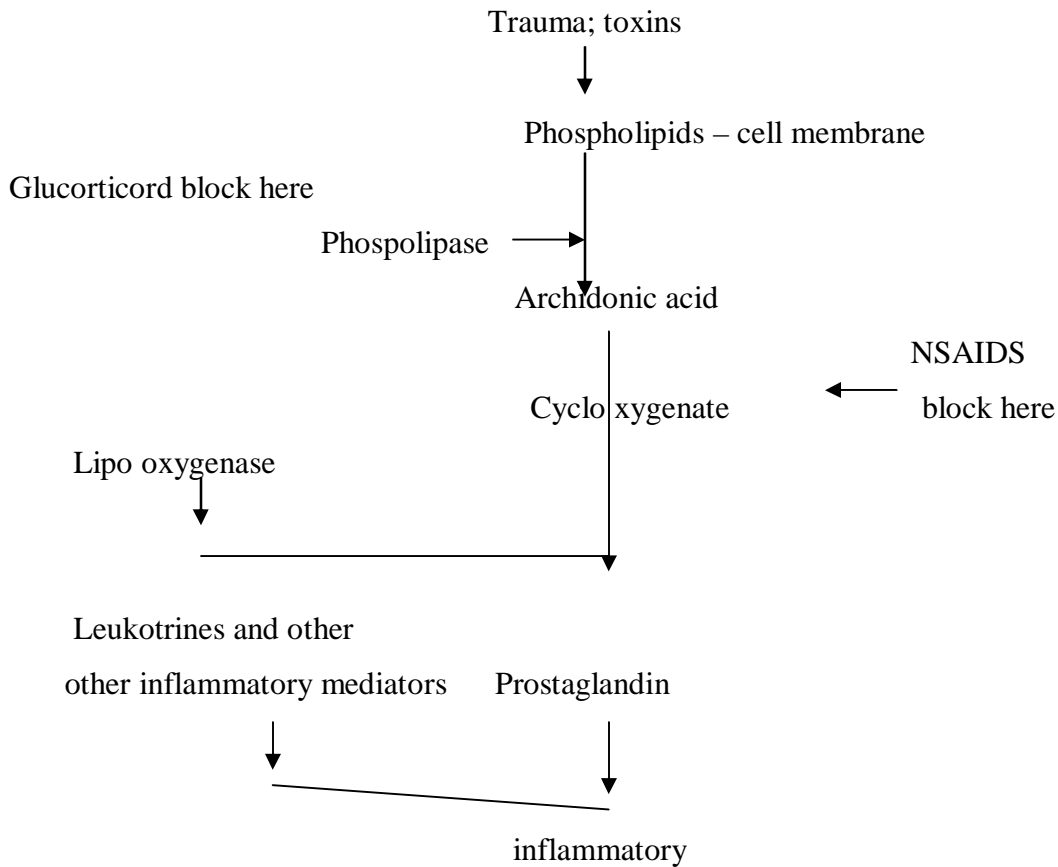
Diprenorphine

- Like nalorphine, it has antagonistic effect and may depress.
- It counteracts depression caused by morphine.
- This agent at twice the dose level of etorphine is capable of immobilizing wild animals.
- Precaution for its administration is same as nalorphine.
- This agent is used mainly in wild and exotic animals to specifically reverse the effect of etorphine.

Route of Administration - I.M. or I.V.

Dosage - 30mg/kg

NON-NARCORTIC ANALGESIC DRUGS



Mechanism of Relieving Pains

SALICYLATE

Aspirin, a salicylate is also known as acetylsalicylic acid.

1. Relief of pains.
2. Reduction of fever (antipyrexia).
3. Anti inflammatory
4. Reduction of platelet aggregation.

Mechanism of action.

- Inhibition of cyclooxygenase which is responsible for synthesis of prostaglandin.

- It diminishes prostaglandin

Clinical Use:

1. Used in all *spp.*
2. Relief of mild to moderate pain resulting from musculoskeletal conditions such as arthritis or hip dysplasia.
3. Post adulticide treatment of heart worm disease
4. Analgesic.
5. Treatment of cardiomyopathy
6. Treatment of edotoxic shock.

Adverse effect

- Gastric users (irritation).
- Cats are susceptible to overdose

Dosage – 10-25mg/kg P.O. in dogs and 10mg/kg in cats.

PHENYBUTAZONE PYRAZOLONE DERIVATES NSAID

1. Analgesia for mild to moderate pain.
2. Anti inflammatory action.
3. Anti pyrexia.

Clinical Uses

- Relief from musculoskeletal conditions in horses and dogs.
- Used in treatment of lameness.
- In dogs, cattle used as analgesia and antipyretic effect.

Adverse effect

Gastro intestinal bleeding and bone marrow suppression

Dosage:

Dogs 22mg/kg P. O. initial dose

15mg/kg I.V. T. D.

Cats 15mg/kg I.V. T. D.

10-14 – mg/kg POBID

ACETAMINOPHEN

- It has an analgesic

- Limited antipyretic and anti inflammatory activity.

Clinical Uses.

The uses are limited in vet medicine because of its risk of potential toxicity and other substitutes.

Dosage in dogs: 15mg/kg P.O. Q.D. is needed.

Adverse effect

- Methemoglobinemia
- Cyanosis
- Anaemia
- Liver damage.

PROPIONIC ACID DERIVATIVES

CARPROFEN

- Approved for oral and injectable used in dogs and cats. t $\frac{1}{2}$ 8hrs.

Mechanism of action

- It works by inhibiting cyclooxygenase

Clinical Use

- Used for postoperative pain from soft tissue and orthopedic pain.

Adverse effect

- Git ulceration
- Bleeding

Dosage

4mg/kg in dogs and cats STD or TID

KETOPROFEN

- Analgesic
- Antipyretic
- Anti inflammatory activity

Clinical Uses

- Mostly used in horses.
- It is also used in dogs and cats.
- Used in treatment of pain and inflammation. Associated with musculoskeletal disorders.
- It is used in post operative and chronic pain in dogs.

Adverse effect

- Git bleeding or ulceration.
- Renal dysfunction.
- Generalized bleeding.

IBUPROFEN

Reported side effects in dogs.

MECLOFENAMIC ACID

Used for treatment of acute or chronic inflammatory disease in horses.

Dog – 2.2mg/kg P.O. BID

Cat – 2.2mg/kg P.O. BID

NEUROMUSCULAR BLOCKING AGENTS

Drugs

The drugs acting to bring about muscle relaxation do these at the following sites:

- Peripherally at the neuromuscular junction
- Centrally in the cerebrospinal axis either directly on the muscle fibre itself to reduce skeletal tone or bring about paralysis or complete relaxation

Indication for the use of Neuromuscular Blockers

- In orthopaedic or intra thoracic surgical procedures to cause relaxation of skeletal Muscle for easier access.
- In reduction of joint dislocation or bone fractures
- \They facilitate endotracheal intubation
- \Endoscopy
- Artificial respiration with adequate relaxation of abdominal and thoracic muscles including the diaphragm.

Caution: These drugs should only be used when facilities for resuscitation are available.

Peripherally acting Muscle relaxants

- They are classified as non depolarizing type or antagonists: act as analogues of Ach
- Agonists (depolarizing) type

Mechanism of action: The peripherally acting neuromuscular blockers are structurally similar to Ach (acetylcholine) thus, they are analogues, these drugs are non depolarizing agents at the neuromuscular junction.

Tubocurarine: It is a prototype of a non-depolarizing muscle relaxants.

Constituent: An alkaloid curare

Sources: Various specie of *Strychnos toxifera*, *Condrodendron tomentosum*

Other uses: hunting the South American Indian use the crude extract “*ourari*” as arrow poison.

Drugs that interact with tubocurarine: aminoglycoside, gentamicin, neomycin inhibits Ach release from the cholinergic nerves by competing with calcium.

Alcuronium: Is a synthetic derivative of the alkaloid toxiferine obtained from *calabash curare*. It has relatively long duration of action of about 70 minutes. Its advantage is it has minimal cardiovascular and histamine releasing side effects due to their virtue of being antagonism to acetylcholine combine with nicotinic receptor and prevent binding of Ach or could cause depolarizing effect and are hence called agonists.

Non depolarizing Muscle relaxants: These drugs prevent depolarization of the muscle membrane and inhibit muscle contraction, thus bring about flaccid paralysis. Because they compete with the Ach they are termed competitive blockers.

Classes:

- Long acting (90-180 minutes)- (1) D-tubocurarine (2) Metocurine (3) dexcurium (4) Pipecuronium (5) Gallamine.
- Intermediate acting(20-40 minutes)- Vecuronium, atracurium
- Short acting (10-20 minutes) Mivacurium

Newer agents of intermediate duration 30-40 minutes example *Rocuronium*

It is excreted unchanged by the kidney

Dose Mg/Kg, I.v	Initial	Dosage increment
Horse	0.05	0.01
Dog	0.1	0.02

Atracurium has minimal vagolytic or sympatholytic properties

Advantage: It could be administered to animals with hepatic or renal failure.

Dose, Mg/Kg	Initial	Dosage increment
Slow I.v	0.15	0.06
Horse		
Sheep, dog, Cat	0.5	0.2

Reading Assignment

Vecuronium

Gallamine triethiodide

NOTE: The action of the peripheral acting muscle relaxants could be counteracted by *neostigmin, endophonium*.

Pancuronium: Is a synthetic steroidal compound that is free from hormonal activity it is about five times as potent as D-tubocurarine but has slow onset of and longer duration of action (120-180 minutes).

Advantages: It does not induce histamine release or significant changes in blood pressure.

Side effects: It has side-effects such as tachycardia in dogs and cats due to vagolytic action.

Pharmacokinetics: Injected by I.v reaches steady state and metabolized by the liver and excreted by the kidney.

Depolarizing Muscle relaxants.

Example: Decamethonium, Succinylcholine or (suxamethonium).

The clinical application of these group drugs is limited because its action cannot be reversed and should not be used except there is provision for artificial respiration facility.

This drug should not be used in conscious animal.

Succinylcholine consists of two Ach molecules linked by their acetyl groups. It is normally broken down rapidly by plasma.

Pseudocholinesterases: It has a rapid onset of action (1-2 minutes) and short duration of action of up to 5 minutes in horses and 25 minutes in the dog. In some species such as cattle, sheep have low plasma levels of the Metabolizing enzymes and thus the action of the drug is greatly prolonged in these species.

Drug interaction: Neostigmine prolongs the duration of action of succinylcholine *antihelmintics* inhibits cholinesterases and thus prolong the duration of action of succinylcholine. *Nifedipine* a calcium blocker also prolong the effect and increases ion muscle relaxing effect.

Uses: With anesthetic agents it is used in obtaining a muscle relaxing effect in all surgery.

- Casting
- Restraining horses
- In dart guns to capture wild animal

Adverse effect: Succinylcholine is associated with depolarization and consists of uncoordinated muscular contraction, salivation and sometimes bradycardia.

Succinylcholine is contra-indicated in cattle

CENTRALLY- ACTING MUSCLE RELAXANT

Centrally acting muscle relaxant (or spasmolytic) reduce skeletal tone by selective action in the cerebrospinal axis. They probably act as the GABA receptors in the C.N.S

Examples include: Mephensin, baclofen, guaiacol glycerol, ether, chlorodiazepoxide and diazepam they do not alter consciousness but reduces skeletal spasticity in a variety of neurologic conditions such as cerebral palsy multiple sclerosis, stroke, spinal cord injury and flexor spasms.

Mephensin:

Chemistry: A propanediol derivative, it inhibits polysynaptic excitation of motor neurons in the spinal cord to produce flaccid muscle paralysis. It is no longer in use because it cause thrombophlebitis.

Guaiacol Glycerol Ether (GGE)

It is a meprobamate-like compound that inhibits polysynaptic spinal reflexes and is currently used as an adjunct in the induction of anaesthesia in horses and cattle. A 10% solution (in water or 5% dextrose) is administered to effect until the animal becomes ataxic. A bolus dose of a general anaesthetic agent such as thiopentone or another would produce recumbency. The dose of thiopentone recommended is (1gm/180kg) is half the normal dose of GGE; it is excreted in urine.

Indications:

(1) In surgery (2) Antitussive (3) decongestant

Benzodiazepines

- Chlordiazepoxide
- Diazepam

They have anxiolytic and sedative properties but only diazepam appears to be widely used in veterinary anaesthesia.

Uses: used in taming of wild animals

- Sedation
- Skeletal muscle relaxation
- Anti-convulsant in status epilepticus
- It is used in combination with ketamine, opioids

The dose in all species is up to 1mg/kg or 1mg/kg-1 commonly administered as injection.

DIRECT ACTING MUSCLE RELAXANTS

Dantrolene is a hydantoin derivative

- It has a direct action on the muscle fibre
- It reduces the amount of calcium release from its stores in the sarcoplasmic

reticulum and hence prevents the excitation-contraction coupling in the skeletal muscle.

Neuromuscular transmission is not affected.

Dantrolene has been used specifically in the treatment of anaesthetic

- induced malignant hyperthermia

Dose Mg/Kg, I.v

Horse, dog up to 2

Pig up to 5

Drugs used for acute local muscle spasm are as follows:

Carisoprodal, Chlorphenesin, Chlorzoxazone Cyclobenzaprine, Metaxalone.