

Antiemetics

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

Classes of anti-emetics

- Demulcents
- Local gastric sedatives and central antiemetics

Demulcents

Soothe inflamed or denuded mucosa or skin.

Molecular weight: High Molecular weight substances and are applied as thick colloidal or viscid e.g. gum acacia, gum tragacanth, 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 benzamides butyrophenones, 5-HT₃ serotonin receptor antagonists.

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

Phenothiazines – acepromazine; chlorpromazine, prochlorperazine and promazine.

Substituted benzamides e.g. metoclopramide, Trimethopbenzamine 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 drugs 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 diphenhymamine to reduce extrapyramidal effect.

Carminatives - They are drugs that aid erretation (expulsion of gas from stomach indicated in ruminal typeni 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

Amitriptyline

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 norepineprine re-uptake is characterized by little effect on dopamine re-uptake.
- Clominpramine 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
- Postinal 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-binding 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 Paroxetine > nor fluoxetine > fluoxetine = Sertraline
- Because of the risk of drug interaction this drug should not be combined with other antidepressants.

Side effects

- Gastro intestinal side effect
- Fluoxetine used for the treatment of lick granuloma caused
- Lethargy
- Hyperactivity

- Polydipsia
- 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, Paraglyline, 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 parkinnsons 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 severe disturbance of the brain function that is 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 Chlorpromazine and thioridazine hydrochloride.

High Potency agents

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

The Antipsychotic 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 is of :

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 (Daicetylmorphine)
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 alkaloid namely Phenanthrene alkaloids and the benzyloquinoline derivatives. The analgesic activity appears to depend upon 7-Phenyl-N-methylpiperidine groupings meperidine derivatives and the methadone compounds assume this structure. The two hydroxylgroup, 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 drugs. The morphine antagonist is prepared by replacement of the CH₃ group on the nitrogen by the alkyl radical – CH₂CH=CH₂.