

Treatment of external parasite

Prepared by Dr. Selamawit Fentahun

Cont...

- Ectoparasites can cause severe irritation and be responsible for loss of condition, disease, and in farm animals ,production deficits due to weight loss, reduced milk yield, or damage to the hide .

Cont...

In many cases, the expected ectoparasitic challenge may be predicted. For example, there will be a rise in **tick** populations in the spring and autumn, increased numbers of **blowfly** in late spring and early summer, and the possible increase of **lice** on winter.

Cont...

- These can be countered by strategic therapeutic and prophylactic use of ectoparasiticides. In contrast, parasitism of intensively housed stock or companion animals, where transmission is by contact, is not 'seasonal'.
- In these situations, control measures should be included in routine hygiene programmes to treat the animals and,

Ectoparasiticide formulation and application

- Ectoparasiticides are available for systemic administration and for topical application by various methods including by dip, spray, 'pour-on', 'spot-on' and dusting powder.
- Different formulations of a drug preparation may be indicated for different parasites

Ectoparasite Treatment

- Ectoparasites can be controlled using a variety of different drugs in a variety of different formulations
 - Sprays
 - Dips
 - Pour-ons
 - Shampoos
 - Oral products
 - Spot-ons

Chemicals Used for Ectoparasite Treatment

- Chlorinated Hydrocarbons
- Organophosphates
- Carbamates
- Pyrethrins and pyrethroids
- Formamidines
- Fipronil
- Avermectin
- Insect Growth Regulators
- Insect Repellents

Chlorinated Hydrocarbons

- One of the oldest groups of synthetic insecticides.
- Reduced usefulness in veterinary medicine
- Resistant to biodegradation (remain in environment for years)
- Includes DDT (dichlorodiphenyltrichloroethane)
- Applied to plants/animals to control insects.
High lipid solubility allows accumulation in fish.
Effects are more intense higher up food chain.

Lindane

MOA- Acts on GABA receptor.

- The only chlorinated hydrocarbon currently used in veterinary medicine today.
- Incorporated in some dog shampoos.
- Kills insects on contact; directly absorbed into insects and their eggs; also a stomach poison for insects
- Can produce harmful side effects in people and pets if absorbed in sufficient quantities.
- Owners should wear gloves, apron, boots
- Lindane should never be used on cats, puppies <3 weeks, lactating animals, or food animals.

Organophosphates & Carbamates

- Decompose readily in environment; do not pose threat to wildlife.
- Among the most widely used of the potent insecticides.
- Also have agricultural applications.
- Organophosphorus compounds inhibit cholinesterase

Organophosphates & Carbamates

- As a general rule, these insecticides should not be used on animals recovering from surgery, sick animals, pregnant animals, or animals considered to be stressed.
- Found in sprays, dips, dusts, and systemic medications
- Carbamates also found in collars and shampoos, with oral products.

Organophosphates & Carbamates

- Adam's Flea and Tick Dip, Spray, and Tick Dust
- Carbaryl (shampoo)
- Sevin (Dust)
- Proban (tablets and liquid)
- Diazinon



Pyrethrins and Pyrethroids

- **Pyrethrins** are natural plant products, derived from flowers
- **Pyrethroids** are synthetic pyrethrins
- Very safe; quick kill
- Adulticide
- Acts on parasite's nerve cell membrane to disrupt sodium channel, which delays polarization and paralyzes the parasite



Pyrethrins and Pyrethroids

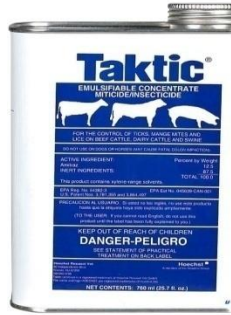
- May have limited residual effects
- Do not use near lakes, ponds, streams (fish easily poisoned with pyrethrins; absorbed through skin)
- Used in small animals primarily for fleas/ticks
- Used in large animals for flies, lice, mites, mosquitos, and ticks
- Commonly used in sprays, dips, pour-ons, and premise sprays.

Formamidines:

- Amitraz is one of the first effective agents available for *Demodex and Sarcoptes* on dogs; Lice, mites, and ticks on cattle; lice, and ticks on sheep; lice and mites on pigs;
- Toxic to cats and rabbits
- Animals may show sedation and incoordination for 24-48 hours after application
- Available in collars, topical treatment, dip, or sponge-on bath.

Cont...

- Can be **very toxic** if ingested by animals or people
- Amitraz toxicosis is treated with supportive therapy and multiple doses of **Yohimbine**
- Owners must be well informed of potential risks of this treatment.



Fipronil

- Interferes with chloride channels of insects, which causing death.
- Adult fleas, ticks, and lice (on contact); controls sarcoptic mange with repeated treatments.
- **Methoprene** is an insect growth regulator, which makes Fipronil effective against flea eggs and larvae.
- Applied topically; not absorbed systemically
- Not for use in puppies or kittens <8 weeks of

Fipronil

- Also marketed as a measured-dose spray product that is applied at a dose of 3 ml/kg body weight.
- Container is calibrated to administer precise amount of insecticide to allow accurate dosing.
- Manufacturer claims that fipronil is unlikely to produce toxicity even if consumed orally.
- Fipronil binds with the dermis, hair follicles, and sebaceous



IVERMECTIN

- **Indications.** **Mites and lice on pigs;** mites, lice, and horn flies on cattle; mites *on sheep; mites on horses*”
- **Contra-indications.** administration to calves less than 12 weeks of age
- pregnancy

Insect growth regulators

Benzoylphenyl urea derivatives
Juvenile hormone analogues

Insect growth regulators (IGRs)

- Are a group of chemical compounds that do not kill the target parasite directly but interfere with its growth and development.
- Insect growth regulators are compounds that affect immature stages of insects and prevent maturation to adults.
- IGRs act mainly on immature stages of the parasite and as such are not usually suitable for the rapid control of established adult populations of parasites

Cont...

- With heavy infestation of adult bloodsucking parasites, IGRs may need to be combined with aduIticides for the first few treatments.
- Where parasites show a clear seasonal pattern, IGRs can be applied at the start of the parasite season as a preventative.
- Based on their mode of action IGRs can be classified as Insect development inhibitors and juvenile hormone analogues
- Insect development inhibitors interfere with development of chitin, which is essential for

Benzoylphenyl urea derivatives

- **Lufenuron**

Indications. Prevention of flea infestation and treatment of

flea allergy dermatitis in dogs and cats

- Fleas take up the drug through the blood and transfer it to their eggs. The formation of larval chitin structures is blocked thereby inhibiting the development of flea larvae.

Cont...

- No viable eggs are produced 24 hours after administration.
- Injectable treatment is given at six monthly intervals to cats and oral treatment is given to dogs or cats once monthly during summer, commencing 2 months before fleas become active.
- Insecticides that kill adult fleas may be required if there is an initial heavy infestation and in cases of

Cont...

- Interferes with chitin synthesis in flea development
- Fleas must bite the animal to be exposed to the drug.
- Fleas continue to lay eggs, but eggs fail to develop normally.
- Lufenuron is distributed to fat and then reaches slowly back into the body fluids, providing a long duration of activity;

Juvenile hormone analogues

- The juvenile hormone analogues, methoprene and pyriproxyfen mimic the activity of naturally occurring juvenile hormones and prevent metamorphosis to the adult stage.
- METHOPRENE
- Indications. Prevention of flea infestation

Insect Repellents

- These preparations are used mainly on horses and cattle to reduce *Culicoides* attack and prevent worry by nuisance flies such as *Musca* and *Hydrotaea*.
- *Preparations containing permethrin* are also effective against biting lice *Bovicola equi* (*Damalinia equi*).
- Time of challenge may vary from year to year, and with preceding and current

Insect Repellents

- Used to repel insects and keep them off of animals
- May be used in combination with pyrethrins and pyrethroids
- Include sprays, and topicals for ear tips
- Some products are insecticides as well as repellents
- Control mosquitoes, flies, and others.

Insect Repellents

- **Butoxypropylene glycol (Fly Repellent)**
 - Used in equine fly repellents because it provides a shine that is of cosmetic value in show animals
 - Incorporated into flea and tick spray products for use in dogs and cats.
 - Can cause dermal irritation if a harness or collar is applied over the area while the haircoat is still wet with spray.

Anti-inflammatory drug

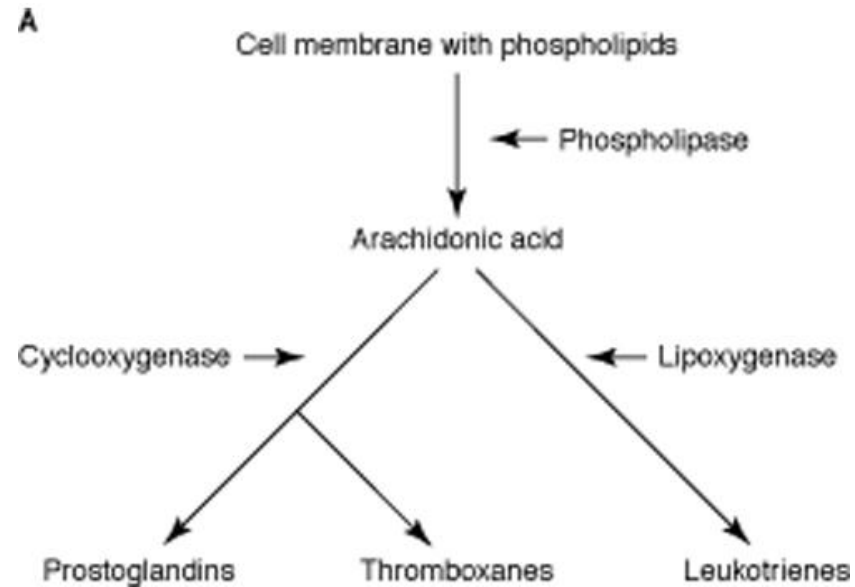
Basic Physiology

- Inflammation is a useful and normal process that consists of a series of events, including vascular changes and release of chemicals that help destroy harmful agents at the injury site and repair damaged tissue
 - Vasodilation increases permeability of blood vessels in the early phase
 - Accumulation of leukocytes, reduced blood flow, chemical release (histamine, prostaglandin, and bradykinin) and tissue damage in cellular phase
- Severe inflammation must be reduced to avoid additional damage to the body

Anti-inflammatory Drugs

- Two main groups of anti-inflammatory drugs

- Steroidal anti-inflammatory drugs block the action of phospholipase
- Nonsteroidal anti-inflammatory drugs block the action of cyclooxygenase



Steroidal Anti-inflammatory

- *Corticosteroids* are hormones produced by the adrenal cortex
- Two groups of corticosteroids used in veterinary medicine are the glucocorticoids and the mineralocorticoids

Glucocorticoids

- Have anti-inflammatory effects due to their inhibition of phospholipase
- Raise the concentration of liver glycogen and increase blood glucose levels
- Affect carbohydrate, protein, and fat metabolism
- Are regulated by negative feedback

Glucocorticoids

- May be categorized as
 - Short-acting (duration of action < 12 hours)
 - Cortisone and hydrocortisone
 - Intermediate-acting (duration of action 12–36 hours)
 - Prednisone, prednisolone, prednisolone sodium succinate, methylprednisolone, methylprednisolone acetate, and triamcinolone
 - Long-acting (duration of action > 36 hours)
 - Dexamethasone, betamethasone, and fluocinolone
- May be given orally, parenterally, or topically

Glucocorticoid Use

- Benefits:
 - Reduce inflammation and pain
 - Relieve pruritus
 - Reduce scarring by delaying wound healing
 - Reduce tissue damage
- Drawbacks:
 - Delay wound healing
 - Increase risk of infection
 - May cause GI ulceration and bleeding
 - Increase the risk of corneal ulceration if corneal damage exists
 - May induce abortion in some species

Key Points About Glucocorticoid Treatment

- Glucocorticoids do not cure disease
- They may help disseminate infectious microorganisms
- Use caution when giving high dosages of glucocorticoids to pregnant animals
- Whenever possible, use the topical form to avoid systemic imbalances
- Use alternate-day dosing at the lowest possible doses to prevent iatrogenic Cushing's disease
- Taper animals off glucocorticoids to prevent iatrogenic Addison's disease
- Do not use glucocorticoids in animals that have corneal ulcers

Nonsteroidal Anti-inflammatory Drugs

- NSAIDs work by inhibiting cyclooxygenase, which has two forms
 - Cox-1 is involved with the stomach
 - Cox-2 is involved with inflammation
- NSAIDs are also referred to as *prostaglandin inhibitors*
- NSAIDs have fewer side effects than glucocorticoid drugs
- Side effects of NSAIDs include GI ulceration and bleeding and bone marrow suppression

Non-steroidal anti-inflammatory drugs (NSAIDs)

⌘ ***Antipyretic, analgesic, & anti-inflammatory agents***

As antipyretics

- └ Reduce body temperature in febrile states

As analgesics

- └ Relieve mild to moderate pain such as dental pain and headache.
- └ Unlike the **opioid analgesics**, they do not cause neurological depression or dependence.

As anti-inflammatory agents

- └ Used to treat conditions such as musculo-skeletal

Cont...

Classification of NSAIDs

Reversible/irreversible action

- ↳ All inhibit COX reversibly, except aspirin

COX₂ selective/ COX nonselective

Note: Acetaminophen is not considered as NSAID

MOA (NSAIDs)

Anti-inflammatory

- ⌘ Inhibits cyclooxygenase (COX) enzyme and hence prostaglandin synthesis
- ⌘ COX-1 is a primarily constitutive in most normal cells and tissues
- ⌘ COX-2 is induced isoform but is also constitutively expressed in certain areas of kidney and brain.

MOA (NSAIDs)

- NSAIDs do not inhibit the lipoxygenase pathways of AA metabolism and hence do not suppress Leukotriene formation.
- All NSAIDs, with the exception of Aspirin, are reversible competitive inhibitors of COX.

Analgesic

- When inflammation causes sensitization of pain receptors to normally painless mechanical or chemical stimuli.
- **Pain that accompanies inflammation** and tissue injury results from local stimulation of pain fibers and enhanced pain sensitivity (hyperalgesia)
- Substances that promote pain transmission
 - Bradykinin & cytokines (such as TNF- α , IL-1, and IL-8)
 - Prostaglandins

Antipyretic

- Formation of cytokines such as IL-1b, IL-6, interferons, and TNF-
- Later increase the synthesis of PGE₂
- Triggers the hypothalamus to elevate body temperature
 - ↳ by promoting an increase in heat generation and a decrease in heat loss

Therapeutic uses (NSAIDs)

- All NSAIDs are **anti-inflammatory, antipyretic and analgesic**, with the exception of acetaminophen, which is largely devoid of anti-inflammatory activity
- **Analgesic**
 - Effective only in pain of low-to-moderate intensity
 - Have less maximal efficacy than opiates but lack the unwanted adverse effects of opiates

- **Antipyretic**

- Reduce fever in most situations

- **Anti-inflammatory**

- In the treatment of musculoskeletal disorders, such as rheumatoid arthritis and osteoarthritis.
 - Generally provide **only symptomatic relief** from pain and inflammation associated with the disease, do not arrest the progression of pathological injury

Adverse Effects of NSAID Therapy

→ ***Gastrointestinal***

⌘ Anorexia, nausea, dyspepsia, abdominal pain, and diarrhea

 } Related to the induction of gastric or intestinal ulcers

⌘ Two proposed mechanisms for the GI ulceration

1. Inhibition of COX-1 in gastric epithelial cells
2. Direct local irritation of gastric mucosa

Drug interactions

- Reduce effectiveness of ACE inhibitors by blocking production of prostaglandins
- May increase GI ulceration when combined with corticosteroids
- Augment risk of bleeding in patients on *warfarin*

Pharmacokinetics & Pharmacodynamics

- Most are rapidly & completely absorbed from the GIT.
- Aspirin begins to acetylate platelets within minutes of reaching the presystemic circulation.
- Most are extensively protein-bound (95% to 99%)

Salicylates

→ Derivatives synthesized for systemic use

Inhibit synthesis of PGs and thromboxanes

Irreversibly acetylates COX-1 and COX-2

pharmacodynamics

- Analgesic Effects (300-600mg)
 - mild to moderate pain
 - Headache, joint and muscle pain, and dysmenorrhea.
- Antipyretic Effects (300-600mg)

Pharmacodynamics

cont'd

- Anti-inflammatory Effects (3-6g)
 - do not influence the progress of disease
 - At higher doses aspirin is an effective antinflammatory in rheumatoid arthritis

Therapeutic uses

⌘ Antipyresis

⌘ Analgesia

⌘ Rheumatoid Arthritis

Adverse effects

- headache, mental confusion, and drowsiness.
- tinnitus and difficulty in hearing.
- hyperthermia, sweating, thirst,
hyperventilation, vomiting, and diarrhea.

Adverse effects cont'd...

Gastrointestinal disturbances

- PGE_2 & PGI_2 ↓
- Gastric ulcerations and/or GI hemorrhage

Reye's syndrome

- └ A potentially fatal disease that causes numerous detrimental effects to many organs, especially the brain and liver.
- └ Disease causes hepatitis with jaundice and encephalopathy

Adverse effects cont'd...

- **Hematologic:** decreased platelet aggregation→ prolonged bleeding time.
- **Hypersensitivity:** rashes
- **Acid-base Imbalance**

Salicylates and Pregnancy

- Avoid administration during the third trimester as they may cause
 - \ Prolonged gestation and complicated deliveries
 - \ Postpartum hemorrhage

Drug Interactions

- ┌ Anticoagulants are potentiated by aspirin by
 - Displacement of the anticoagulants from plasma proteins
 - anticoagulant effect of aspirin.
 - dosage of drugs such as coumarin and heparin should be reduced in patients taking aspirin.

Drug Interactions cont'd...

- Aspirin decreases effect of loop diuretics and spironolactone.
- Phenobarbital increase the metabolism and excretion of aspirin
- Antacids can alkalize urine enough to increase salicylate clearance.

Treatment of Aspirin poisoning

- Inducing emesis or gastric lavage.
- Appropriate infusion measures to correct abnormal electrolyte balance and dehydration.
- Alkalization of the urine

Acetaminophen (Paracetamol)

Pharmacologic effects:

It has **analgesic and antipyretic actions similar to those of aspirin** but only weak anti-inflammatory

It appears to be an **inhibitor of PG synthesis in the brain** which explains its analgesic and antipyretic activity.

It is much **less effective than aspirin as an inhibitor of the peripherally located PG** biosynthetic enzyme system that plays such an important role in inflammation.

Available without a prescription and is used as a common household analgesic

It does not affect platelet function or increase bleeding time

It is not considered to be an NSAID.

Acetaminophen cont'd...

- ♣ **Indication:** used as substitute for the analgesic and antipyretic effects of NSAIDs for patients with
 - ‖ Gastric complaints/risks
 - ‖ Prolongation of bleeding time is not desirable
 - ‖ Anti-inflammatory action of NSAIDs is not required
 - ‖ Analgesic/antipyretic of choice for children with viral infections (due to the risk of Reye syndrome with aspirin)

Acetaminophen cont'd...

⌘ Pharmacokinetics

- ⌋ Rapidly absorbed from GIT
- ⌋ Metabolised in liver (half-life 2-4 hours)

Acetaminophen cont'd...

⊖ Adverse effects

At normal therapeutic doses, it is virtually free of significant adverse effects.

With large doses it causes hepatic necrosis

Hepatic necrosis: a very serious and potentially life threatening condition, can result.

High dose acetaminophen may results in an increased risk of gastrointestinal toxicity equivalent to NSAIDs.

Drug interaction

Oral *N*-acetyl cysteine (NAC) is an Antidote

Patients with **hepatic disease, viral hepatitis, or a history of alcoholism** are at higher risk of acetaminophen induced hepatotoxicity

Relatively safe though cross placenta

Alcohol, barbiturates and phenytoin induce enzyme
decrease the effectiveness of acetaminophen.

Acetic acid derivatives

Indomethacin

Antiinflammatory, analgesic, and antipyretic

Pharmacologic effects: *(10-40 time more potent anti-inflammatory than aspirin)*

- | Inhibit COX non-selectively
- | May also Inhibit phospholipase

Indomethacin

θ **Pharmacokinetics**

- Has excellent Oral bioavailability
- 90% bound to plasma proteins and tissues
- $t_{1/2}$: 4 -12 hrs

Indomethacin

Therapeutic uses

- ‖ Conjunctival inflammation (ophthalmic preparation)
- ‖ Gingival inflammation is reduced after administration of indomethacin oral rinse
- ‖ Rheumatoid arthritis when Aspirin is ineffective
- ‖ Osteoarthritis
- ‖ Acute gout

Note: Because of its toxicity and side effect, it

Indomethacin

Adverse effect

- ‖ Gastrointestinal complaint
- ‖ CNS effects: 25%-50%
 - ‖ Headache, light-headedness, Seizures, confusion, psychosis, hallucinations, and suicide
- ‖ Hematologic reactions
 - Neutropenia, thrombocytopenia, and aplastic anemia
- ‖ Hypersensitivity reactions
 - Asthma (aspirin- sensitive patients may exhibit cross-reactions to indomethacin)

Diclofenac

- Diclofenac is the most commonly used NSAID
- **Pharmacological Properties**
 - Its potency against COX-2 is greater than that of several NSAIDs.
- **Pharmacokinetics**
 - Rapid absorption, extensive protein binding
 - short half-life(1-2 hrs)

Diclofenac Cont'd...

♣ Therapeutic Uses

- Long-term symptomatic treatment of rheumatoid arthritis and osteoarthritis,
- Short-term treatment of acute musculoskeletal pain and postoperative pain
 - In combination with misoprostol (to reduce the frequency of GI ulcers)

Diclofenac Cont'd...

Common Adverse Effects

- Modest, usually reversible
- CNS effects, rashes, allergic reactions, fluid retention, and edema,
- Not recommended for children, nursing mothers, or pregnant women.

Propionic Acid Derivatives

θ **Include: Ibuprofen and** naproxen

└ **Pharmacological Properties**

└ nonselective COX inhibitors

└ **Therapeutic uses**

└ Rheumatoid arthritis and Osteoarthritis

└ **Apply to long-term treatment because they are better tolerated.**

Ibuprofen

└ Pharmacokinetics

- └ Absorbed rapidly
- └ undergoes hepatic metabolism and renal excretion

└ Adverse Effects

- Better tolerated than aspirin and indomethacin
- Treatment with ibuprofen in patients with increased cardiovascular risk
- use of ibuprofen concomitantly with aspirin may decrease the total anti-inflammatory effect.

Naproxen

└ Pharmacokinetics

- └ Absorbed fully when administered orally.
- └ Is almost completely (99%) bound to plasma proteins

└ Common Adverse Effects

- └ GI adverse effects
- └ CNS side effects (drowsiness, headache, dizziness, sweating, fatigue, depression, and ototoxicity)

The Fenamates

-Mefenamic and meclofenamic

- ‖ No clear advantages over other NSAIDs and frequently cause GI side effects
- ‖ **Therapeutic use**
 - ‖ pain in soft-tissue injuries
 - ‖ Dysmenorrhea
 - ‖ rheumatoid arthritis
 - ‖ osteoarthritis
- ‖ Not recommended in children or pregnant women

Fenamates cont'd...

♣ Pharmacokinetic Properties

- Absorbed rapidly and have short duration of action.

♣ **CI:** patients with a history of gastrointestinal disease

♣ Adverse Effects and Precautions

- **GIT:** Diarrhea is relatively common
- Hemolytic anemia is a potentially serious but rare side effect.
- Discontinue If diarrhea or rash occur

Flunixin meglumine

- Inhibits cyclooxygenase
- Used in cattle and horses for musculoskeletal and colic pain
- Is a potent analgesic, antipyretic, and anti-inflammatory

COX-2 Selective NSAIDs

- └ Non-selective COX inhibitors
 - └ **Cause frequent GI side effects**
- └ Selective COX-2 inhibitors
 - Celecoxib, *parecoxib* and etoricoxib
 - Do not affect the activity of COX-1
 - Inhibits COX-2 which is believed to be dominant in inflammatory sites.
 - Hence, they cause inhibition of PG synthesis in inflammatory sites while the gastric cytoprotective function of PG is left intact

⊖ **Adverse Effects**

- Use of COX-2-Selective inhibitors is associated with increased cardiovascular hazards

NSAIDs During pregnancy

- ‖ Not recommended during pregnancy, particular 3rd trimester
- ‖ Acetaminophen is safe during pregnancy

Chemotherapy of neoplastic diseases

Cancer therapy

- Conventional methods for cancer therapy in animals are surgery, radiotherapy, and chemotherapy.
- These techniques need not be used in isolation, indeed the combination of surgical management of a primary mass with chemotherapy directed at systemic disease is the most logical and potentially effective way of managing malignant disease.
- Surgery is the most effective form of treatment⁸³

Cont...

- The use of radiotherapy in veterinary medicine is limited by the availability of and access to radiotherapy facilities
- The main role of radiotherapy is as a local treatment for malignant tumours, which cannot be controlled by surgery alone.
- Radiotherapy cannot be used to treat widespread disease because of its toxicity, although local lymph nodes may be included in treatment fields

Cont...

- The major indication for chemotherapy is in the treatment of systemic malignant disease such as lymphoma and other lymphoproliferative and myeloproliferative diseases.
- The tumour cells in these diseases are reasonably chemosensitive and the widespread nature of the disease necessitates a systemic form of therapy.
- Chemotherapy is not effective against large solid primary tumours of skin, soft tissues, or bone but may have a beneficial role as an adjunct to surgery in the

Cytotoxic drugs

1. Alkylating drugs
2. Antimetabolites
3. Antitumour antibiotics
4. Vinca alkaloids
5. Platinum compounds

Cytotoxic drugs

- Cytotoxic drugs are classified according to their characteristic sites or modes of action.
- Most cytotoxic drugs act upon the processes of cell growth and division.
- These drugs are potent and potentially dangerous and extreme care is required in their use. Careful consideration must be given to the pharmacology and toxicity of the drug, the spectrum of drug activity, and the condition of the patient.

Cont...

- The main indications for cytotoxic drugs in veterinary medicine are management of lymphoproliferative and myeloproliferative disorders including leukaemia, lymphoma (lymphosarcoma), and multiple myeloma.
- Cytotoxic drugs are of little value as sole agents in the management of large solid tumours such as mammary carcinoma or fibrosarcoma.

Cont...

- They may have a palliative role as adjuncts to surgery or radiotherapy in the prevention or management of metastatic disease.
- In this role chemotherapy is complementary to surgical excision of the primary tumour with the actions of the drugs directed at microscopic disease residual at the primary site or elsewhere in the body in the form of micrometastases.

Cont...

- Generally, the use of cytotoxic drugs in combination protocols is favoured as the most effective approach; by combining different drug classes that have different mechanisms of action greater tumour cell kill may be achieved without increasing normal tissue toxicity.

Cont...

- For example, combinations of cyclophosphamide (alkylating agent), vincristine (vinca alkaloid), and prednisolone (corticosteroid) are widely used in the treatment of canine and feline lymphoma.

Alkylating drugs

- In veterinary medicine, alkylating drugs are the most widely used in cancer chemotherapy. They act by interfering with DNA replication.
- **Cyclophosphamide** is widely used in the treatment of lymphoproliferative diseases in cats and dogs. Use in the treatment of multiple myeloma has been reported.
- Cyclophosphamide may also have a role as an adjunct to surgery in the treatment of certain solid carcinomas and sarcomas.

Cont...

- Cyclophosphamide is converted to active alkylating metabolites by the liver and primarily excreted by the kidney. One of the metabolites, acrolein, may cause a necrotising haemorrhagic cystitis.
- **Chlorambucil** is the slowest acting and least toxic of the alkylating drugs. It is primarily used for treatment of lymphoma, in the treatment of chronic lymphocytic leukaemia and multiple myeloma.

Cont...

- The use of chlorambucil in the treatment of polycythaemia vera has been described.
- Myelosuppression is reversible on discontinuation of the drug.
- chlorambucil is biotransformed in the liver and excreted in the urine as inactive metabolites

Cont...

- **Busulfan** has a selective action against granulocytes and is almost exclusively used in the treatment of chronic granulocytic leukaemia.
- Use in the treatment of polycythaemia vera has been described.
- Myelosuppression is the main side effect although pulmonary fibrosis may occur rarely.
- Busulfan is excreted in the urine as inactive metabolites.

Antimetabolites

- Antimetabolites interfere with DNA and RNA synthesis by interaction with enzymes.
- **Fluorouracil** has been used in the treatment of carcinomas of the mammary gland, gastrointestinal tract, liver, and lung in dogs, but is at best palliative.
- In addition to myelosuppression, fluorouracil causes neurotoxicity, manifest as cerebellar ataxia and seizures. These effects are transitory in dogs *but fatal in cats and* **fluorouracil is**

Cont...

- Fluorouracil is metabolised in the liver and other tissues. Inactive metabolite are excreted in the urine.
- **Methotrexate** competitively inhibits the enzyme, which is essential for the synthesis of purines and pyrimidines.
- Methotrexate may be used in the treatment of lymphoproliferative and myeloproliferative disorders.
- Its use has also been described in osteosarcoma and other sarcomas.

Cont...

- Even at low doses, many dogs will show side-effects of severe diarrhoea.
- Methotrexate is primarily excreted unchanged by the kidney and renal tubular necrosis may occur with high-dose regimens. Myelosuppression and gastro-intestinal ulceration are common side-effects.

Antitumour antibiotics

- These drugs act by forming a stable complex with DNA and interfering with the synthesis of nucleic acids.
- **Doxorubicin** is an anthracycline antibiotic, and is one of the most effective of the cytotoxic drugs.
- In veterinary medicine, doxorubicin is used to treat lymphoproliferative and myeloproliferative disorders.
- It is also a palliative in soft tissue and osteogenic sarcomas and in carcinomas of

Cont...

- **Epirubicin** is a structural analogue of doxorubicin. The tumoricidal activity of both drugs is similar but epirubicin is reported to be less cardiotoxic than doxorubicin.
- The indications for epirubicin are essentially as for doxorubicin.

Vinca alkaloids

- These drugs are plant alkaloids. They bind to microtubular proteins, causing metaphase arrest thus inhibiting mitosis. They may also cause enzyme inhibition.

Cont...

- **Vincristine** is the most widely used vinca alkaloid in veterinary medicine.
- The main indications are in the treatment of lymphoproliferative disorders. And also in the treatment of soft tissue sarcomas and carcinomas.
- Vincristine causes virtually no myelosuppression, Constipation may result from long-term therapy.

Cont...

- **Vinblastine** is less frequently used than vincristine. Its uses include treatment of lymphoproliferative disorders and mast cell tumours.
- Unlike vincristine, vinblastine causes myelosuppression, and will also cause severe perivascular reactions.
- vincristine and vinblastine undergo hepatic metabolism and biliary excretion.

Platinum compounds

- Platinum compounds inhibit protein synthesis by cross linking strands of DNA.
- These are potent drugs with a broad spectrum of activity
- They may cause severe toxicity which limits their use in veterinary medicine
- **Cisplatin** has been used, by intravenous infusion, in the treatment of osteosarcoma, soft tissue sarcoma, and various carcinomas.

Cont...

- Cisplatin is nephrotoxic, causing acute proximal tubular necrosis. Vomiting and myelosuppression also occur.
- Pretreatment hydration recommended.
- Treatment with this drug should be supervised by specialists familiar with its use.
- ***Cisplatin*** can cause severe pulmonary reactions in cats and its use is contra-indicated in this species.

Cont...

- **Carboplatin** is a second generation platinum analogue with a spectrum of antineoplastic activity similar to cisplatin.
- Carboplatin has a much shorter elimination half-life than cisplatin and is significantly less nephrotoxic however, myelosuppression can be severe.
- Carboplatin has been used in the treatment of canine osteosarcoma and some carcinomas. It