Purine antagonists

The 6-thiopurines (6-mercaptopurines, 6-mp; azathioprine; thioguanine, 6-TC.) are purines analogues.

- The purines anatagonists are effective antineoplastic and immunosuppressive agents.
- 6- TC- and 6-mp. Were the first thiopurines.

Mechanism of action

The thiopurines are phosphorylated in cells to their respective corresponding monoribonucleotides, which act as purine antagonists thereby inhibits DNA and RNA synthesis.

Pharmacokinetics – The 6- thiopurines are not well absorbed orally.

- The 6- thiopurines are metabolized by xanthine oxidase
- Allopurinol is administrated in patient given the 6-thiopurines to reduce hyperuricaemia,
- It is important to reduce the dose of 6-mp to 1/4 -1/2 of allopurinol to avoid toxic accumulation of the drug
- Thioguanine is not substrate for xanthine oxidase
- It undergoes S-methylation and its dose need not be adjusted if used with allopurinol

Therapeutic uses

- Mecaptopurines are used as adjunctive therapy of lymphosarcoma in the dog acute lymphoblastic leukaemia, and severe rheumatoid arthritis
- It has marked effect on T-lymphocytes, suppresses cell-mediated immunity
- Used as a second or third-line –immunosuppressive agent used in the treatment of immune-mediated diseases in dogs.

Other purine antagonists are:

- Fludarabine
- Cladribine
- Pentostatine

Student should endeavour to read more on these drugs.

Pyrimidine antagonists

Pyrimidine antagonists have varied applications as antineoplastic, antifungal and antipsoriatic agents. 5- Fluorouracil, cytarabine, capecitabine, gemcitabine.

Mechanism of Action

- Pyrimidine analogues are phosphorylated in cells to the corresponding deoxy nucleotide (e.g. cytarabine is converted to cytosine arabinoside triphosphate) that blocks D.N.A. synthesis.
- 5-fluorouracil (5-Fu) elicits its action via inhibition of thymidylate synthetase , an enzyme required for the synthesis of thymidylic acid, a precursor of D.N.A.
- The drug is administered intravenously.

Adverse effect

- Myelosuppression
- Intestinal epithelial damage.
- Neurotoxicity in both dogs and cats.

Therapeutic uses

- Brea**st** cancer
- Gastrointestinal cancer

Dose: - 50 – 200mg/m^2 B.S.A I.V. Once weekly.

Capecitabine : is an oral administered fluoropyrimidine carbamate, cytotoxic activity, undergoes bio activation to 5fu, the drug is tumor specific.

Capecitabine ⟶ 5-Fu- uracil

Then **Metabolized to** to ά-fluoroB-alanine passed in urine

*****Students should read more on the other members of this class of drugs.**

ANTITUBULIN AGENTS

This agents are sourced from the a plant, they are derived from the periwinkle plant (*Vinca rosea, linn*), and *Catharanthus roseas)*

Mechanism of action

They are thought to bind microtubular proteins and inhibit formation of mitotic spindle, thus suspending mitosis in *metaphase* in:

The plant contains vinca alkaloids that are cell cycle specific for M – phase, thus, inhibiting mitosis and causing cell death.

Examples of such drugs are:- ***vincristine, vinblastine, vinorelbine, and vindesine***

Pharmacokinetics

- The vinca alkaloids are not absorbed orally
- They better administered intravenously
- The drug becomes rapidly distributed to tissues, except C.N.S.
- The vinca alkaloids are 75% protein bound
- It is metabolised in the liver and excreted unchanged in urine and bile respectively

Therapeutic uses

- Vincristine is used in combination with cyclophosphomide, prednisolone and cytarabine.
- Used in treatment of lymphoproliferative disorders
- Transmissible venereal tumors.
- Mast cell tumors in dogs
- Acute lymphoblastic leukaemia in children
- Wilms tumor (a malignant renal tumor in children.

Therapeutic use of vinca alkaloids

- Vinorelbine shows a promising effect in the treatment of advanced non-small cell lung cancer.
- Vinblastine is used in testicular carcinoma

Therapeutic advantages

- The vinca alkaloids have low toxicity for normal cells.

  Thus, are relatively safer.

Combination therapy

- Initial dose

Vincristine 0.5-0.7mg/m^2 B.S.A I.V once weekly

Cyterabine 100mg/m^2 B.S.A or SC daily for four days

Cyclophosphomide 50mg/m^2 BSA P.O every alternate day

Prednisoline 20mg/m^2 BSA P.O twice daily for one week, then half dose daily

Maintenance dose:

Vincristine O.5mg/m^2 BSA l.V second

Cyclophosphamide 50mg/m^2 BSA P.O every second day

Prednisolone 20mg/m^2 BSA P.O every second day.

Adverse effects

- Bone marrow depression
- Peripheral neuropathy caused vincristine
- Alopecia
- Neurotoxicity
- Neuromuscular weakness
- Constipation
- Severe local blistering
- Extravascular leakage

ANTITUMOUR ANTIBIOTICS

Certain antibiotics, isolated from various strains of *Streptomyces* and *Aspergillus* possess antitumour properties, mainly by direct interactions with D.N.A, leading to disruption of D.N.A function

The antitumour antibiotics are cell-cycle specific.e.g. anthracyclines (doxorubincin, daunorubicin, idarubicin)

Actinomycin D (dactinomycin, chlomopeptide); epirubicin (mitozantrone), aclarubicin mitomycin, streptozotocin, and plicamycin

Mechanisms of action

The anthracycline antibiotics (e.g. doxorubicin)

- The drugs intercalated with D.N.A to inhibit D.N.A replication.
- Cleave D.N.A chains
- Induce formation of radicals, which damages the cell membrane bleomycin glycopetides chelate ferrous iron and interact with oxygen, resulting in oxidation of iron and

generation of free radicals (superoxide or hydroxyl), which cleave and fragment D.N.A *Bleomycin* is specific for cells in G_2 phase of the cell-cycle.

- Actinomycin D interacts with D.N.A helix and blocks transcription by R.N.A polymerase.
- Plicamycin exerts its cytoxicity through restriction of D.N.A-directed R.N.A synthesis.

Pharmacokinetics

- Dactonomycin, doxorubicin, daunorubicin is administrated intravenously
- Extravasations can lead necrosis
- Daunorubiun are inactivated in the gastrointestinal tract if administrated bleomycin is administrated by a number routes, subcutaneously, intramuscularly intravenously, and intracavity
- The plasma has protein binding and widely distributed
- Dactinomycin is concentrated in the liver where is partially metabolized.
- Most of the parent drugs and their metabolized are slowly excreted via bile and urine.

Therapeutic uses of antibiotics

- The antitumour antibiotics inhibit rapidly proliferating cells normal and neoplastic origin and are beneficial in a wide variety of tumors.
- Doxorubicin and daunorubicin are the most active agents used in soft tissue tumours
- Oesteosarcoma could be treatment by this class of lungs
- Carcinomas of lungs
- Mammary gland.

Dose

Actinomycin_ D.

Dog, cat	O.5 -1.5mg/m^2 B.S.A, every 2-3 weeks or up to once weekly	

Doxorubicin

Dog	30mg/m^2 BSA	l.V every 3weeks
Cat	25-30mg/m^2 B.S.A.	l.V every 3-6 weeks

Dunorubicin

Cat	15-30mg/m^2 B.S.A	l.V. every 3weeks

Bleomycin

Dog, cat	10-15mg/m^2B.S.A	l.V, once weekly.

Adverse effects

Vomiting, stomatitis, diarrhea, erythema, and desquamation of skin, alopecia, and bone marrow depression. Daunorubicin and doxorubicin produce cardiotoxicity.

- Plicamycin causes toxicity to, osteoclasts this prevents their re-absorption and lowers plasma calcium concentration in hypercalcacmic patients, especially those with bone tumours.

Hormonal agents

Some growth of some cancers are hormone dependent. Some hormones oppose the growth of the cancer, thus the hormones are termed antagonists some agents inhibit the synthesis of the relevant hormones.

Most steroid – sensitive mammary and prostate cancer have specific receptors to which, the steroid hormones bind.

Glucocorticoids

Examples (prednisolone, prednisone, dexamethasone)

They inhibit:

- Proliferation of lymphocyte.
- Leukaemias
- Lymphomas used also used in C.N.S lymphoma.
- Canine lymphosarcoma and mastocyoma.

Adverse effect:- immuno-suppression, loss of skin colafen, muscule weakness, pot belly, glucose intolerance cushingoid syndrome.

Oestrogen

Oestrogen (e.g. diethylstil besterol, fosfestrol, a prodrug activated by acid phosphatase in prostatic tissue to yield stiboestrol, and oestradiol)

Therapeutic use of Oestrogen

- Perianal adenoma.
- Prostatic hypertrophy in male dogs.
- Carcinomas are probably androgen dependent.
- Oestrogen with orchiddectomy which suppress androgen product in testis by feed back suppression of gonadotrophins (FSH and LH).

Adverse effects

- Feminization
- Fluid retension
- Alopecia
- Myelosuppression (aplastic anaemia and thrombocytopenia)

Androgens

Androgens (e.g. testosterone, dromastanslone). These are used in treatment of canine mammary carcinoma in combination with oophorectomy.

Gonadotrophin – releasing hormone agonist

Prostate carcinomas and perianal adenomas are androgen – dependent and can be treated by orchidectomy, or by gonadorelin analogue. Buserelin, goserelin, leuprorelin, cyproterone .

Indication

- Surge of testosterone secretion can occur in patients with prostate cancer.
- Goserelin is implanted intramuscularly to form a depot.
- Octreotide is used in treatment of hormones secreting tumors of the gastrointestinal glands. e.g. (vipomas, glucogonomas, carcinoid, syndrome, gastrinoma).

Hormones antagonist

- Tarmoxiphin, flutamide.
- Used to treat mammary tumor
- Progesterone – endometrial cancer dose 20mg/day.

ANTI-VIRAL DRUGS

OVERVIEW

- There is a search for drugs that inhibit virus specific function.

- Viruses are sub-microscopic, obligate, intracellular pathogenic entities consisting essentially of nucleic acid (either RNA or DNA) enclosed in protein coat called the capsid with no metabolic machinery of their own.
- There are draw-backs when using an antiviral agent or drugs, the major draw-backs are;
    a) Highly specific selective toxicity is difficult. These drugs could cause injury to the host.
    b) A substantial amount of multiplication of the virus would have taken place before symptoms manifestation.
    c) Control of viral infections is expensive.

Inhibition of viral adsorption and entry into host cells.

Immunoglobulins

- Types M, G, A and E.
- Definition protein molecules that possess antibody activity.

Mechanisms of preventing viral infections.

- Coating the viruses cell surfaces receptors (polypeptide) that are needed to attach to the host cells.
- The coated viruses are rendered more susceptible to phagocytosis.

Dose: 0.025-0.25ml/kg I.m of gramma globulin.

Diseases that could be prevented are: *Measles, hepatitis, rabies, poliomyelilitis*.

There are Hyper-immune globulins specific against particular viruses (eg. Maxagloban P derived from canine serum is used in dogs and other susceptible species against canine distemper, canine viral hepatitis and parvovirus.

Side Effects

- Danger of hypersensitivity reactions serum sickness.