ADAMANTANAMINES

Examples: amantadine, rimantadine.

Chemistry: they are tricylic admantanamines.

Mode of action: It blocks viral membrane matrix protein, M_2 which functions as an ion channel.

Pharmacokinetics:

- Both amantadine and rimantadine are well absorbed orally.
- Amantadine distributes throughout the body and readily penetrates into C.N.S.
- Rimantandine does not cross the blood-brain barrier to the same extent.
- About 90% of amantadine is excreted unchanged into urine 2-3 days

  t ½ = 16hours
- Rimantadine is extensively metabolized by the liver has a half life of 30 hours.

Uses:

Amantadine, rimantadine is used primarily for influenza prophlaxis during an epidemic to limit household contacts. It is also used in turkeys.

Adverse effects

- Minor neurologic symptoms in humans.
- Dizziness and ataxia
- Hallucination.

INHIBITION OF VIRAL REPLICATION

Guanidine and hydroxybenzylimidazole –

- Inhibit the replication of certain R.N.A enteroviruses.
- Inhibit of formation of *R.N.A polymerase* at concentrations that appear to be harmless to the host.

- Inhibition of early protein synthesis

Ribavirin

Example (tribavirin) is a synthesis nucleoside similar in a structure to guanosine

Mode of action

Altering of a nucleotide pools or interfering with the synthesis of viral MR.N.A.

It inhibits a wide range of D.N.A and R.N.A viruses

Uses:

To treat influenza and infections pneumonia and bronchitis –used to treat lassa fever, arena virus infection.

Side effects:

- Teratogenic in laboratory animals
- Haemolysis
- Bone- marrow depression
- Anaemia
- C.N.S and gastro intestinal disturbances

PYRIMIDINE NUCLEOSIDES

Idoxuridine (5-iodo-2-deoxyuridine. I D U) was the first pyrimidine antimetabolite to be used as an anti-virus drugs.

Mode of action

It competes with thymidine and disrupts its function so that synthesis of matured virus is prevented.

Clinical use of IDU

- Topical therapy of herpes simplex keratoconjunctivitis

- Treatment should continue for 5-7 days

Irifluridine, a halogenated thymidine analogue has replace Idoxuridine in the topical treatment of keratoconjuctivities and is applied at 1% eye drop preparation.

Cytarabine is an analogue of the naturally occurring nucleoside 2- deoxycytidine

Mode of action

Cytarabine enters the target cells and undergoes the same phosphorylation reactions as the physiologic nucleoside to the cytosine arabinose triphosphate this inhibits D.N.A polymerase and interferes with viral D.N.A synthesis

The disadvantages of this drug:

Its triphosphate derivatives are protein inhibitor of D.N.A polymerase in mammalian cells.

5-fluorouracil and 5-bromouracil

These are pyrimidine nucleosides that effectively block the replication of D.N.A viruses in the cell culture systems.

PURINE NUCLEOSIDES

Vidarabine

- Is the least toxic and one of most effective of the purines analogue
- It is an adenine analogue
- It inhibits the D.N.A polymerase of the virus more effectively than mammalian D.N.A polymerase.

Therapeutic uses

- 3% ophthalamic ointment vidarabine is used to treat ocular herpes and vaccinial keratities.

  Vaccinial keratitis continues for 5-7 days after healing to prevent recurrent infection

- Vidarabine penetrates into the brain, and thus use systematically for life threatening herpes simplex encephalitis and disseminated neonatal herpes virus infection.
- It could be used in fluid as intravenous infusions of 10-15 mg /kg/day over 12hrs for 10 days.

ACYCLOVIR

Other examples classified as guanosine analogue are **acyclovir, ganciclovir**, **famiciclovir, cidofovir.**

Mode of action

The acyclovir is converted to monophosphate in the cell by herpes virus encoded enzyme, thymidine kinase. The virus infected cells are most susceptible. The host cells kinases then converts the monophosphate to triphosphate, which in turn inhibits viral D.N.A. polymerase 10-30 times more than it does to the host cells D.N.A. polymerase.

Pharmackinetics

- After administration either by I.V., oral or topically in ointments or ophthalmic preparations.
- It forms the pro-drug called the valaclovir, is more readily absorbed from the gastrointestinal tracts than the acyclovir.
- Only 20% of the drug administered orally would be absorbed and reaches peak plasma level in 1-2 hours.
- The drug is widely distributed and reaches a concentrations in the cerebro-spinal fluid that are 50% of those in the plasma.
- It penetrates the cornea well and reaches the kidney, in the kidney the concentration is 10 times higher than the plasma.

- Acyclovir is partially metabolized to an inactive form
- Excretion into the urine occurs both by glomerular filtration and tubular secret in its plasma half-life is 2-3 hours.

Therapeutic uses

- Acyclovir is used in the treatment of herpes simplex infection (genital herpes, mucocutaneous herpes, and herpes encephalitis).
- In human, it is used prophylactically in patients that are to be treated with immuno-suppresant or radiotherapy, and patients that frequently suffer genital herpes infection.

Adverse effects

Side effects are minimal but the side effects associated with the drugs are nausea, vomiting, diarrhea, headache and rashes.

Renal dysfunction.

Nucleoside reverse transcriptase inhibitors.

Zidovudine (Azidothymidine) (AZT) this is an analogue of thymidine, a dideoxynucleoside.

Mode of action

Zidovudine was the first drug used to treat HIV. The drug inhibits viral reverse transcriptase (RNA dependent D. N. A. polymerase). So that synthesis of viral

D. N. A. is inhibited and replication is markedly decreased.

Pharmacokinetics

- Zidovudine is well absorbed orally.
- Peak plasma concentration occurs at 30 minutes. The bioavailability of he drug is 60-80 percent.

- It becomes distributed to most tissue including the cerebro-spinal fluid and central nervous system.
- Most of the drug is metabolized to inactive glucuronide in the liver.
- 20 percent is excreted unchanged in the urine.

Therapeutic uses.

- Currently approved in the treatment of HIV
- Used to prolong life of HIV infected patients.
- Given to HIV infected parturient mother and then to neonate for 6 weeks.

Dose in -

Adults 500mg/day P. O. in 2-4 divided doses.

Children 1.80mg/m^2 (maximum 200 mg) P. O. every 6-8 hours.

Adverse effects – Zidovudine is toxic to bone marrow, producing *anaemia_neutropaenia_*and delayed neurotoxic reactions (convulsions encephalopathy) and myopathy.

Other example of dideoxynucleosides used in the treatment of HIV are **Didanosine, Zalcitabine, stavudine, lamivudine.**

Other example of drugs used to treat HIV are ;

RETROVIRAL PROTEASE INHIBITORS

HIV requires an aspartate protease enzyme which is enclosed in its genome for the final step of viral proliferation so the Retroviral protease inhibitors inhibit this final step thus, used to prevent proliferation and treatment of the virus.

Chemistry of protease inhibitors

They are peptidyl analogues that reversely interfere with the process of assembly of non-functional virions

Example of Retro-viral protease inhibitors

1) Ritronavir, 2) Saquinavir
3) Indivinir 4) Nelfinar and 5) Amprenavir

Therapeutic disadvantages of Retro-viral protease inhibitors

- Resistance develops against this group of drugs in months to years

Clinical uses

It is advisable to combine protease inhibitor with AZT, combinations previously used are as follows:

- **Saquinavir** with AZT, this results to better effect which is more effective than one drug used alone
- Thus , triple therapy is more effective then double therapy
- Currently it is advisable to combine a protease inhibitor with two reverse transcriptase inhibitors such as **Didanonsine, Zalcitabine , Stavudine, Lamivudine.**

Adverse effects of protease inhibitors

- Gastro- intestinal disturbance
- Asthenia
- Headache
- Parasthesia
- Dizziness

And exacerbation of diabetes

They inhibit cytochrome P-450 dependent oxidations and also cause lipodystrophy and hyperglycaemia

NON –NUCLOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Examples **Nevirapine, elavirdine, efavirenz** these are selective, non competitive transcriptase.

Therapeutic advantage: They lack effect on the blood forming elements and lack of cross resistance with nucleoside reverse transcriptase inhibitors

Phosphonoacetric acid

It inhibits herpes virus D.N.A polymerase, effective in birds and mammals at subcutaneous of 500mg/kg/day the clinical potential is still unknown

HOST IMMUNE MODULATORS : INTERFERONS

Interferons are family of inducible glycoproteins produced by mammalian cells and now by recombinants DNA technology in bacteria as the recombinant organism and the (genes from human leukocytes)

Types of interferons

The classification of interferons is based on antigenic and physical properties. The interferons are as follows:

1) IFN-α (Leukocyte interferon, type 1)
2) IFN –β (fibroblast interferon, type 1)
3) IFN-γ (immune interferon, type 2)

IFN-γ

The IFN-γ (immune interferon, type 2) constitutes a family of hormones involved in growth of cell and regulation modulation of immune reaction. The IFN-γ is produced mainly by the T-

lymphocytes as part of immune response to both viral and non viral antigens (including bacteria, polysaccharides, and a range of polymeric chemicals and other cytokines)

Mechanism of action.

Interferons are associated with induction of host cells, enzyme (e.g. protein kinase, 2',5'-oligoadenylate synthetase, and a phosphodiesterase) that inhibit viral RNA translation and ultimately lead to degradation of viral mRNA and tRNA and it possess anti-proliferative due to its effect on the RNA and DNA.

Therapeutic uses

In feeder calves, IFN-α has been found useful against infections bovine rhinotracheitis.

- Used in cats to treat non-neoplastic FeLV disease.
- IFN-α is recommended or indicated for hairy cell –leukaemia, kaposis sarcoma.
- Papilloma virus
- Used in herpes simplex
- Used also management herpes zoster.

Clinically interferons could be combined with acyclovir or vidarabine.

- Used in chronic hepatitis "B" a d "C" infections.
- Interferons could be administered intralesional to cause regression of genital warts.
- IFN-γ improves treatment of severe leishmaniasis.

Dose of interferons

IFN is given intravenously at the dose range of 10^6-10^9 units daily.

Adverse Effects:

- Fever
- Fatigue

- Headache
- Weakness
- Myalgia
- Bone marrow depression.
- Cardiovascular disturbances.

Interferon Inducers

Several substances induce interferon – production and are used to prevent treatment of viral infections – and neoplastic disease.

High molecular weight inducers e.g.

a) Polyriboinosinic
b) polyI-poly C

Low molecular weight inducers

a) tilorone
b) amino-bromo-phenyl-pyrimidinol.

Clinical Use:

They are used in prevention of viral hepatitis.

ANTIFUNGAL DRUGS

Instructional Objectives

At the end of the period of instruction students should be able to:

a) List various classes of antifungal drugs frequently used in veterinary practice.
b) List examples of various classes of antifungal drugs
c) Suggest the used of antifungal drugs based on their pharmacokinetics and therapeutic uses

d) A student should also be able to categorically state the relevance of this subject area to the veterinary practice.

OVER VIEW

Fungal infections (mycoses) are classified into two types: topical (superficial), which affects the skin and mucous membranes, and systematic which affect areas as the blood, lungs, or C.N.S. patients with fungal infection are treated with oral, topical, or parenteral drugs that are suitable for these infections used in veterinary medicine are as following

1) Polyene
2) Imidazole
3) Antimetabolites
4) Superficial agents

FUNGAL DISEASES OF VETERINARY IMPORTANCE

Dimorphic fungal infections:- Includes

a) Blastomycosis

B) Cryptococcosis

C) Histoplasmosis and

d) Coccidioidomycosis

Superficial Forms are on the skin and they *cause Dermatophytosis Candidiasis*

*Trichophytosis***:**

The fungal is an eukaryotic organism and is filamentous with hyphae or intracellular yeast

Sporothrix schenkii produce an external coating or slime layer that encapsulates the cells and cause them to adhere to one another or form clumps together the fungal cells are complex rigid

and contain chitin and polysaccharides it precludes staining with gram staining and forms barrier to drug penetration. The cell of fungi is complex and contains sterols