ANTIFUNGAL DRUGS

Treatment of fungal infections generally has been less successful than that of bacterial infections largely because eucaryotic fungal cells are much more similar to human cells than are bacteria. Many drugs that inhibit or kill fungi are therefore quite toxic for humans. In addition, most fungi have a detoxification system that modifies many antifungal agents. Antifungal drugs that inhibit DNA, RNA, or protein may have the same effects on human (animal) cell.

Polyenes (macrolide antibiotics)

Polyenes are macrolide antibiotics and include drugs such as nystatin amphotericin B. They bind to ergosterol, i.e., disrupt cell membranes. There are a number of polyenes, but amphotericin B is the only one with a level of toxicity that renders it suitable for systemic antifungal therapy in humans and animals. Nystatin is effective against *Candida albicans*.

Azoles (imidazoles, triazoles)

Imidazoles have two nitrogens in the ring and include clotrimazole, ketoconazole, miconazole, econazole. Triazoles have three nitrogens in the ring and include fluconazole, itraconazole, and voriconazole. The azoles inhibit cytochrome P-450 dependent enzymes; this enzyme lanosterol to 14-dimethyllanostenol during the synthesis of ergosterol. The azoles are effective in mucocutaneous candidiasis, dermatophytoses, and some systemic mycoses.

Grisans

Griseofulvin is a grisan derivative produced by *Penicillium griseofulvum*; it is fungistatic antibiotic which binds to microtubular proteins and interferes with microtubule spindle formation, thereby inhibiting fungal cell mitosis **(antimitotic antibiotic).** It may also act as an inhibitor of nucleic acid synthesis. Griseofulvin is useful in dermatophytoses.

Nucleoside analogs

5-fluorocytosine is a fluorinated pyrimidine that enters fungal cells by the action of cytosine permease and is deaminated to 5-fluorouracil which is incorporated into RNA in place of uracil, with resulting impact on protein synthesis. In addition, further metabolism of 5-fluorocytosine produces a potent inhibition of thymidylate synthetase which causes inhibition of DNA synthesis. Flucytosine is a narrow spectrum of antifungal and is active against *Cryptococcus neoformans*, *Candida spp* and some dematiaceous moulds. When used alone, drug resistance is an important cause of therapeutic failure. To overcome this problem, flucytosine is used in combination with amphotericin B.

Allylamines

Examples of allylamines include Naftifine and terbinafine. **Allylamines** inhibit the activity of squalene epoxidase, an enzyme required for the production of ergosterol, the principal sterol. Decreased synthesis of ergosterol and accumulation of squalene produces a toxic effect on fungus. Allylamines are broad spectrum antifungals, and are particularly effective against dermatophytes.

Echinocandins (semisynthetic lipopeptides)

Examples of echinocandins include caspofungin, micafungin and anidulafungin. Echinocandins inhibit fungal 1, 3-β-glucan synthase which is required for the synthesis of 1, 3-β-glucan, a major component of fungal cell walls. Since mammalian cells do not contain 1, 3-β-glucans, these antifungal drugs are selectively toxic for fungi. Caspofungin has a limited spectrum of action; it is effective against *Aspergillus species* and most *Candida species* and it is also effective against *Pneumocystis carinii*. The antifungal spectrum of caspofungin, micafungin and anidulafungin appears to be similar.

Morpholines (e.g., amorolfine)

Morpholines inhibits ergosterol biosynthesis; amorolfine's fungistatic activity correlates with the depletion of ergosterol which is essential for the functioning of the fungal cell membrane. It is used to treat onychomycosis and dermatophytoses.

Nucleoside-peptides (e.g., Nikkomycin Z)

Nikkomycin Z inhibits chitin synthase; interferes with the synthesis of fungal cell wall polysaccharides. It also potentiates the effect of flucytosine, a number of azole compounds and echinocandins. Although nikkomycin Z was shown to be highly effective against murine coccidioidomycosis, histoplasmosis and blastomycosis, further clinical trials are required to confirm its therapeutic effectiveness in mycoses.

Substituted pyridine (e.g., Ciclopirox olamine)

Ciclopirox olamine alters membrane transport, damages the fungal cell membrane and interferes with metabolism of target cells by affecting mitochondrial electron transport processes during energy production. Ciclopirox olamine, which is applied topically, has broad-spectrum antifungal activity. It is fungicidal for dermatophytes, Candida albicans, Malassezia species and fungal pathogens causing onychomycosis.

Iodides

Sodium iodide and potassium iodide have been used for many years to treat animal mycoses, but their mode of action is not well understood.

Enhancement of immune responses against fungal pathogens has been suggested. A direct antifungal effect through interference with enzymes essential for fungal cell metabolism may contribute to the activity of iodides. Prolonged treatment with iodine compounds is often required to clear mycoses. Sodium iodide has been used to treat sporotrichosis and also nasal aspergillosis in dogs. Prolonged administration can lead to iodism in some animals; avoiding residues in milk and meat, requires careful use in food-producing animals.

ANTIVIRAL DRUGS

Antiviral drugs are generally only effective prophylactically or in the early stages of disease when viral replication is occurring. When feasible, immunization is the preferred method for controlling viral infections in humans and animals. Although antiviral chemotherapy is now a well-established part of human treatment regimes, its place in veterinary medicine is less well defined. Cost, the necessity for rapid and reliable diagnosis before commencing treatment and the circumstances in which antiviral drugs can be used therapeutically have curtailed this form of therapy in animals. Because viruses utilize the host cell's biosynthetic systems for replication, development and delivery of antiviral therapy present many challenges relating to efficacy and toxicity for the host. Most antiviral drugs have narrow therapeutic margins and the efficacy of antiviral chemotherapy is further complicated by viral latency. Virus replication occurs in sequential steps: attachment, penetration, uncaoting, biosynthesis, assembly, release. Effective antiviral drugs inhibit virus-specific events related to virus replication rather than host cell synthetic activities.

Effects of viral infections on the host cell

1. Viral infections in which there is no progeny virus are produced (abortive infection)
2. Viral infections in which host cell may be altered antigenically but is not killed, although progeny virus are released (persistent infection)
3. Latent viral infections (e.g., in case of tumour viruses)
4. Lytic infection (death of host cells)

Antiviral therapy is aimed at preventing virus entry into host cells, interfering with uncaoting, genome replication or assembly and release of virus from host cells.

The antiviral agents available against viruses can be classified as: (a) nucleoside analogs,

(b) non-nucleoside polymerase inhibitors, (c) protease inhibitors, (d) neuraminidase inhibitors, (e) M2 channel blockers, and (f) interferons.

Nucleoside analogs

Nucleoside analogs cause selective inhibition of viral replication by binding better to viral DNA polymerase, rather than to the cellular DNA polymerase; and by being utilized more extensively in virus-infected cells due to the more rapid synthesis of DNA in infected cells. The commonly used nucleoside analogs are acyclovir (ACV), valacyclovir, penciclovir, and famciclovir, ganciclovir, azidothymidine (AZT), ribavirin, and dideoxynucleosides (dideoxyinosine, dideoxycytidine, stavudine, and lamivudine).

Acyclovir has selective action against herpes viruses, such as herpes simplex virus (HSV) and varicella zoster virus. Other nucleoside analogs include idoxuridine, trifluorothymidine, fluorouracil, and adenine arabinoside. Recently, many other nucleoside analogs have been evaluated as antiviral agents for treatment of infections caused by HIV, hepatitis B virus, and herpes viruses.

Non-nucleoside polymerase inhibitors

Non-nucleoside polymerase inhibitors include foscarnet and related phosphonoacetic acid. These inhibitors inhibit replication of viruses by binding to the pyrophosphate binding site of the DNA polymerase to block binding of nucleotides. Foscarnet specifically inhibits DNA polymerase of all herpes viruses and reverse transcriptase of the HIV. The compound has also shown antiviral activity against hepatitis B virus. Other non-nucleoside polymerase inhibitors include Nevirapine, delavirdine, and efavirenz.

Protease inhibitors

Saquinavir, indinavir, ritonavir, nelfinavir, and amprenavir are some of the examples of protease inhibitors. These agents act specifically on the unique structure of HIV protease, which is essential for the production of a functional HIV.

Neuraminidase inhibitors

Zanamivir (Relenza) and oseltamivir (Tamiflu) are the antiviral compounds with clinical efficacy against both the influenza A and B viruses. They are potent inhibitors of the influenza

Neuraminidase. Without production of the enzyme neuraminidase, the hemagglutinin of the virus binds to sialic acid on other viral particles, forming clumps and thereby preventing release of virus particles.

Ion channel blocking compounds

The anti-influenza drugs amantadine and rimantadine inhibit virus replication at an early stage in the replicative cycle of influenza A viruses. The mechanism of action of these antiviral drugs relates to virus uncaoting shortly after endocytosis of virus by the host cell. Following attachment to host cell sialic acid moieties on cell surface glycoproteins by means of influenza envelope glycoprotein spikes or haemagglutinins, the virus is endocytosed. At this early stage of its replication cycle, the virus is contained in a membrane-bound compartment, the endosome. As part of its normal function, the endosome becomes acidified. The low pH causes a conformational change in the virion haemagglutinin protein, and fusion of the virion envelope and the endosomal membrane occurs, releasing the nucleocapsid into the cytoplasm of the host cell. However, in the presence of amantadine, the matrix protein, M1, does not dissociate from the ribonucleoprotein which remains in the cytoplasm instead of entering the nucleus. The M2 protein in the nucleocapsid seems to form a polymeric tube-like structure through which hydrogen ions from the acidified endosome enter the virion and dissociate M1 from the ribonucleoprotein.

By interfering with the ion channel function of the M2 protein, amantadine (or rimantadine) inhibits acid-mediated dissociation of the ribonucleoprotein complex early in replication, a process essential for uncaoting of the single-stranded RNA genome. Amantadine and rimantadine are useful in reducing severity of influenza A infection if taken within 48 hours of exposure. They are also useful as prophylactic agents in treatment of influenza A infection. Amantadine is toxic to the central nervous system.

Interferons

On the basis of antigenic characters, cell of origin and other properties, there are three type of interferon: interferon alpha (IFN-α), interferon beta (IFN-β), and interferon gamma (IFN-ɣ). **IFN-α** is produced by macrophages, monocytes, and B lymphocyte following induction by suitable viruses. It is chemically a non-glycosylated protein and at least 16 subtypes of IFN-α have been identified. It has a maximal antiviral activity. **IFN-β** is produced by fibroblasts and epithelial cells following stimulation by viruses or polynucleotides. It is a glycoprotein and has intermediate antiviral activity.**IFN-ɣ** is a cytokine produced by activated T cells and NK cells on stimulation by antigens or by mitogens in the later part of infection.

Chemically, it is a glycoprotein and is concerned with immunoregulatory and proliferative functions as lymphokines than as an antiviral defense. Interferons are poor non-antigenic or poorly antigenic, hence there is no routine serological tests available for their detection and estimation. Interferons by themselves have no direct action on viruses but have antiviral properties in adjacent, non-infected cells of the same species rendering them refractory to viral infection. Interferon does not act on cells of unrelated species. When cells are exposed to interferon, they produce a protein known as 'translation-inhibiting protein, TIP, which selectively inhibits translation of viral mRNA, without affecting host cell mRNA. The TIP is a mixture of at least 5 different enzymes – a protein kinase, an oligonucleotide synthetase, an RNAase, a phosphodiesterase, and nitric oxide synthetase, all together block translocation of viral mRNA into viral proteins. Interferons are not activated until they bind to double-stranded RNA. Interferons are now being increasingly used for treatment of chronic hepatitis B and C virus carriers who are at risk of progressing to cirrhosis and hepatocellular carcinoma.