Anti viral

Against herpes viruses

Against herpes simplex& varicella zoster virus

- Acyclovir
  - •inside viral infected covert into acyclo-guanosine monophosphate by viral thymidine kinase
  - •converted by host kinase into triphosphate which is incorporated into DNA & competitively inhibits viral DNA polymerase in viral DNA synthesis (cause premature termination of proviral DNA chain)
  - •Topically: ointment for herpetic keratitis, cream for oral& genital herpes simplex
  - •orally: 4/d treatment and prevent of genital & oral herpes and for treting herpes zoster (20% absorbed from gut)
  - •IV:severe herpes simplex or varicella zoster in immuno-suppressed patients and for cases of herpetic encephalitis
  - •eleminated by kidney, safe in pregnancy
  - •SE: GI (nausea, diarrhea) ,CNC(headache, neurotoxicity in large doses) , renal crystal precipitation and damege (IV)
- valacyclovir
  - oral, better absorbed from intestine than acyclovir ,more bioavailable (60%) ,converted into acyclovir by first pass liver
- Famiciclovir and penciclover
  - •given oral
  - •Famiciclovir is converted to penciclover in liver
  - •Famiciclover:used for herpes zoster
  - •penciclovir: similar to acyclovir to inhibit viral DNA synthesis, used for genital or oral herpes
- others for herpetic keratitis
  - •Vidarabine(adenine arabinoide): ointment
  - • Trifluridine(trifluorothymidine) : eye drops

    Both decrease viral DNA synthesis
  - •Idoxuridine: Eye drops,ointment, it is incorporated into DNA instead of thymidine so decrease viral DNA synthesis

    SE: stinging sensation, allergy

Against cytomegala vjrus

- Ganciclovir
  - •like acyclovir
  - •converted inside host cell into active triphosphate
  - •IV for CMV retinitis (may given intra vitreous or ocular implant
  - •orally 6-9% absorbed from gut
  - •cause neutropenia, anemia, thrombocytopenia (due to BM depression)
- Foscarnet
  - •non-nucleoside derivative
  - •IV for ganciclovir resistant CMV and for acyclovir resistant herpes zoster
  - •eliminated by kidney
  - •SE:renal toxicity, hypocalcemia,CNS(hallucination, seizures)
- Cidofovir
  - •phosphorylated inside host cells into active diphosphate
  - •IV for CMV retinitis
  - •longer intra-cellular t1/2 than ganciclovir
  - •nephrotoxic(reduced by probenecid)
- Fomiversen
  - •bind to viral mRNA to inhibit protein synthesis& virus growth
  - •intravitreous innection for resistant cases
  - • slowly eliminated from retina
  - •systimic anti-CMV therapy also neded
  - •toxicity is iritis, vitritis,rise IOP

Antiviral drugs for hepatic viral infections

Interferons IFNs

- •protective glycoproteins that are produced by virally infected cells to make other normal cells resist viral infection
- •IFN-alpha is produced by leukocytes, IFN-beta is produced by fibroblasts , and IFN-gamma is produced by lymphocytes
- •IFN-alpha (2a, 2b) are prepared by DNA recombinant biotechnology

MOA:○stimulation of intracellular enzymes in virally infected cells leads to inhibition of translation of viral mRNA by ribosomes; also inhibit formation of viral mRNA

○stimulate cellular immune defences against virus, and also against some cancers:•IFN-a (2b, or 2a) is used SC or IM against : hepatitis B or C virus infections, Kaposi"s sarcoma, severe herpes zoster, and intra-lesional injection into viral genital warts.

•IFN-a (2b): used in some cancers e.g. chronic myeloid leukemia, hairy cell leukemia, malignant melanoma, & metastatic renal cell cancer.

SE:•Flue-like illness : this occurs within few hours of administration; it is a common reaction

•CNS : causing fatigue and depression. Severe anorexia occurs , leading to weight loss

•CVS : hypotension and cardiac arrhythmias may occur

•Bone marrow depression may occur leading to neutropenia or thrombocytopenia.

Lamivudine

Against respiratory viruses

Amantadine

- •inhibit viral un-coating
- •used for prevention or early treatment of influenz A2
- •effective orally, eliminated by kidney, avoided in renal failure and epilepsy (increase brain excitability and cause seizures
- •useful in parkinsonism

Rimantadine

- Rimantadine is similar but largely eliminated by liver and lesser extent by kidney

Neuraminidase inhibitors

inhibit release of new viral progeny occurs by budding and block viral entry into host cells

- Oseltamivir(Tamiflue): •orally, prodrug activated by liver or gut , eliminated by kidney in urine
  - •used in prevention and treatment of influenza A or B or virulent H5N1 of avian virus
  - •SE: nausea and vomiting
- zanamivir(Relenze): inhalation for prevention and treatment of influenza A or B , cause bronchospasm , avoid in asthma

Ribavirin

- •decrease viral mRNA synthesis ,effictive against many RNA and DNA viruses
- •inhalation for Respiratory Syncitial Virus (infant) which cause acute bronchiolitis (high mortality)
- •oral with subcutaneous IFN-alpha-2b for chronic hepatitisC (effictive together)
- •eliminated by kidney in urine, avoided in RF
- •SE: fatigue,rash,nausea and hemolytic anemia ,avoided during pregnancy (teratogenic in animls)

Aganist HIV

Nucleoside Reverse Transcriptase Inhibitors

•converted to triphosphate form by host enzymes to become active.

•inhibits reverse transcriptase (RT) competitively, & causes premature termination of proviral DNA chain.

- Zidovudine (Azidothymidine)
  - •analouge of thymidine
  - •orally
  - •eliminated by liver& kidney
  - •CSF about 60% of plasma
  - •SE: Neutropenia, anemia and sometimes thrombocytopenia due to bone marrow depression (additive to ganciclovir), CNS, Myopathy, G.I.(common) hepatomegaly with cholestasis and lactic acidosis.
- Didanosine
  - •analogue of adenosine
  - •SE:peripheral neuropathy& pancreatitis
- Zalcitabine
  - Cytidine analogue, long acting, used with zidovudine
  - •SE: peripheral neuropathy , rarely pancreatitis
- Emtricitabine
  - cytidine analogue , for HIV
- stavudine
  - •thymidine analogue, intracellular phosphorylation is reduced by zidovudine (avoid combined use), excreted by kidney, short t½ .
  - •SE:peripheral neuropathy (avoid use with neurotoxic anti-HIV drugs e.g. zalcitabine or didanosine)
- Lamivudine
  - •cytidine analogue, long acting & least toxic, Best additive to zidovudine or stavudine & is best given in combination, Less dose in RF.
  - •useful against hepatitis B virus ,can be given with or without interferon IFN-alpha 2b; alternative is oral adefovir or tenofovir .

Non-Nucleoside RTIs

- •Nevirapine , Delaviradine, Efavirenz
- •Don't require intracellular phosphorylation, Directly inhibit viral RT of HIV.
- •Less S.Es : Maculopapular rash
- •Liver toxicity in ~ 5% with Nevirapine

Protease inhibitors

- •Indinavir, Ritonavir, Saquinavir, Nelfinavir
- •Inhibits viral protease that converts large viral polyproteins into smaller polyproteins for virions.
- •S.Es : G.I (most common) Renal stones (with indinavir) Liver toxicity (with ritonavir and saquinavir)

Fusion inhibitors

- • givenSC
- •Enfuvirtide: binds to surface glycoprotein of HIV, preventing its attachment and penetration into host cells.
- •used in combinations if resistance to other anti-HIV drugs develops

Integrase Inhibitors

- •Raltegravir is the first of new class of antiretroviral drugs (integrase inhibitors).
- •Raltegravir inhibits the final step in integration of stand transfer of the viral DNA into our own host cell DNA

→ Note:- result in HIV treatment are obtained with combination of 4 drugs : 2NRTIs + 1NNRTI +Protease inhibitor

*lipodistrophy:- interference with carbohydrate and lipid metabolism .with prolong Therapy in combination

* lipodistrophy syndrome:- include fat redistribution insulin resistence and dyslipidemia

→ fat redistribution after chronic use including loss of fat from extremities and its accumulation in abdomen and base of neck (buffalo hump)