UNIVERSITY OF NAIROBI
SCHOOL OF MEDICINE
DEPARTMENT OF PHARMACOLOGY

ANTIVIRALS

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- Virus- obligate intracellular parasites

CLASSIFICATION

1. AGENTS FOR TREATING HERPES SIMPLEX AND VARICELLA ZOSTER VIRUSES
    1. Acyclovir
    2. Valacyclovir
    3. Famciclovir
    4. Penciclovir
    5. Trifluridine
2. AGENTS USED FOR THE Rx OF CTYTOMEGALOVIRUS INFECTIONS
    1. Ganciclovir
    2. Valganciclovir
    3. Cidofovir
    4. Foscarnet
3. AGENTS USED FOR THE RX OF HEPATITIS
    1. Lamivudine – HBV
    2. Adefovir – HBV
    3. Interferon alpha, 2a, 2b, interferon alfacon 2b, pergilated interferon 2a, 2b -HCV, HBV
    4. Ribavirin – HCV, Influenza A, B, parainfluenza, RSV, HIV1, Paramyxoviruses
    5. New agents – entecavir, clevudine, emtricitabine, theradigon-HBV, thymosin alfa 1
4. AGENTS USED FOR THE RX OF INFLUENZA
    1. Amantadine, rimantadine, zanamavir, oseltamavir.
5. ANTIRETROVIRALS.
    1. NRTI- Zidovudine (AZT), stavudine (d4T), didanosine (ddl), zalzitabine (ddc), lamivudine (3TC), abacavir, tenofovir, emtricitabine, amdoxovir
    2. NNRTI- Efavirenz, delvirdine, nevirapine
    3. PI – Saquinavir, ritonavir, lopinavir, indinavir, nelfinavir, amprenavir, atazanamavir, tipranavir, fos-amprenavir

6. Fusion inhibitors = enfurvitide
    - Under development -entry inhibitors – maraviroc, maturation inhibitors, intergrase inhibitors.
7. Others -
    1. Palivizumab – RSV agents
    2. imiquimod – HPV agents.

ANTIVIRALS MECHANISMS

1. Viral adsorption – enfurvitide (HIV), gamma globulins, dextran SO4, rec sol CD4, sulfated

polysaccharides, docosanol (HSV), Palivizumab

2. Penetration and uncoating – amantadine, rimantadine, - influenza A, interferon alfa (uncoating)
3. Early protein synthesis – formiversen- CMV
4. Nucleic acid synthesis – purine and pyrimidine analogues, RTI (reverse transcriptase inhibitors), intergrase inhibitors, forscarnet (CMV), entecavir.
5. Late protein synthesis – methisazone (variola), Pis, interferon, ribavirin
6. Packaging and assembly – rifampicin (vaccinia), puromycin, interferon
7. Viral release – neuraminidase inhibitors – oseltamavir, zanamivir, --influenza.

ACYCLOVIR (Zovirax)

- An acyclic analogue of guanosine

MOA

- It effectively inhibits viral DNA polymerase and DNA replication causing premature viral DNA chain termination. The action is selective for viral DNA
- First converted to acyclovir monophospate, by viral thymidine kinase readily. Then to di and triphosphate form which is the active metabolite. Acyclovir triphosphate competitively inhibits deoxyGTP.

ANTIVIRAL ACTIVITY

- Primarily effective for herpes simplex, but has some activity on varicella zoster virus, CMV, EB viruses

P'KINETICS

- Given both orally and parenterally, IV, and topically
- Oral absorption is variable and incomplete, bioavailability 15-20%. Unaffected by food
- Protein binding is minimal 20%. well distributed throughout the body. CSF levels are 50% of plasma levels
- Minimally metabolized, mainly eliminated by glomerular filtration and tubular secretion. A small proportion is excreted as an oxidized inactive metabolite
- T1/2 3-4 hrs in normals, but upto 20 hrs in anuric pts
- Readily cleared by haemodialysis but not peritoneal dialysis
- Topical application produces concentration in herpetic lesions, but no systemic levels by this route

CLINICAL USES

1. Genital herpes – initial infections, less effective in recurrent infections
2. Topically for herpetic keratoconjuctivitis
3. Intravenous for herpetic encephalitis. Superior to vidarabine here
4. Accelerates healing in herpes zoster
5. Prophylaxis in leukemia and transplant pts
6. Herpes labialis – only modestly effective

DOSES

- Doses 200mg 3-5 times daily PO,
- For VZV higher doses 800mg 8 hourly
- IV 5mg/kg 8 hourly
- Topically – 5% cream
- Cross resistance with valacyclovir, famciclovir, ganciclovir
- In resistance alternatives are foscarnate, cidofovir, trifluridine

ADVERSE EFFECTS

- Minimal
  - headache
  - GIT -nausea, diarrhea, vomiting occasionally
  - less frequently – fatigue, skin rash, fever, alopecia, depression
  - Rarely renal dysfunction, neurologic toxicity like tremors, delirium, seizures

VALACICLOVIR (valtrex)

- L-valyl ester of acyclovir
- Given orally and rapidly metabolized to acylcovir giving 3-5 times plasma levels than acyclovir. Oral bioavailability is 54%
- Indicated for herpes zoster and simplex of skin and mucous membranes – 1mg BD x 7-10 days
- 1 day rx of oral-labial herpes – 1gm BD
- Prevention of CMV in organ transplant pts.
- Prevention of recurrent genital herpes with 1 daily dose of 500mg- 1000 mg
- zoster 1gm TID x 7 days

ADVERSE EFFECTS

- Minimal
- GIT effects
- rash
- Rare – agitation, dizziness, headache, anaemia and neuropenia
- AT higher doses- confusion, hallucinations, seizures, GIT intolerance and thromobotic microangiopathies.

FAMCICLOVIR (famvir)

- A diecetyl ester prodrug of 6-deoxypencyclovir, an acyclic guanosine analogoue, given orally. Rapidly metabolized to pencyclovir
- Effective against HSV 1 & 2, VZV, EBV & HBV
- Acts like acyclovir but does not cause chain termination. Achieves higher intracellular concentrations and longer actions
- Oral bioavailability of 70%. Intracellular half lifes 10 hrs in HSV1 infected cells, 20 hrs in HSV2 Infected cells and 7 hrs in VZV infected cells in vitro
- Excreted in the urine mainly
- Indicated in genital herpes, 250 mg TID X 7-10 days
- 1000mg BD for a day of recurrent herpes
- Herpes labialis – single dose 1500mg, or 750 mg BD for 1 day
- VZV
- Well tolerated but pts may have headache, diarrhea, nausea.

PENCICLOVIR

- A guanosine analogue available for topical use. 1% cream for herpes labialis in immunocompromised

DOCOSADANOL

- A saturated 22-carbon aliphatic alcohol
- Inhibits fusion btw HSV envelope and plasma membrane. Used topically as 10% cream, x 5 daily.

TRIFURIDINE

- Trifluorothymidine, a fluorinated pyrimidine nucleoside. Inhibits DNA synthesis in HVS1, HSV2, vaccinia and some adenoviruses
- Converted to triphosphate form by host cell enzymes, then completes with thymine triphosphate for the DNA polymerase for incooperation into viral DNA
- Used as topical application, 1% solution in keratoconjuctivitis and recurrent epithelial keratitinitis due to HSV 1 &2.
- Alone or in combination with interferon alfa in acyclovir

GANCYCLOVIR (cytovene)

- A synthetic nucleoside analogue of guanine
- Inhibit DNA polymerase
- ANTIVIRAL ACTIVITY
  - HSV 1& 2, HHV2, VZV, EBV, CMV; invitro activity against hepatitis B virus

P'KINETICS

- Poorly absorbed orally, bioavailability of 3-5% in fasting and 6-9% with meals
- P orally is 1 mcg/ml, IV peak is 11.5 mcg/ml
- Well distributed in the whole body
- CSF levels 24-70% those of the plasma intravitreal levels 10-15% those of plasma
- Half life 2.5 – 3.6 hrs by IV and 3-7 hrs by oral route
- Oral form 86% excreted in stool and 5% excreted in urine. IV form is wholly excreted in urine unchanged

CLINICAL INDICATIONS

1. CMV retinitis – IV 5mg/kg 12 hrs x 14- 22 days, then maintanance 5mg/kg/d IV or 1gm TID PO
2. Sustained release gancyclovir implant vitrasert, usually with oral gancyclovir to prevent systemic CMB disease
3. Other forms of disseminated CMV treat as for CMV retinits. Need for maintainance in CMV encephalitis and radiculopathy
4. CMV prophylaxis – 1mg TID PO. Prevents primarily CMB retinitis

ADVERSE EFFECTS

IV form

- Neutropenia if <25% stop drug
- Thrombocytopenia in 2-8%
- CNS toxicity in 10-15% - headache, dizziness, seizures, confusion, coma
- Hepatotoxicity in 2-3%
- GIT Intolerance

Oral form

- Neutropenia in 18%
- Anaemia in 35%
- Serum createnine > 1.5 mg/dl in 73%
- Fever

- Rash
- Contraindicated in pregnancy

INTERACTIONS

1. AZT – concomittant the use increases risk of neutropenia
2. DDI – serum levels increase
3. Probenicid – increases its levels by 50%
4. Synergistic activity with foscarnet in CMV and HSV
5. Use with caution with drugs that inhibit replication
6. Nephrotoxic drugs increase risk of renal dysfunction e.g AZT, Imipenem/cilastatin.

Tuesday, 15th June 2010

CIDOFOVIR (vistide)

- Nucleoside analogue of guanosine

Chemistry & MOA

Viral activity- in vitro activity against CMV, VZV, EBV, Less effective on HSV, ade

P'KINETICS

- Given IV
- Prebeneial blocks tubular secretion increasing concentration of 40-60%
- Doesn't appear in CSF
- T1/2 17-65 HRS
- Excreation in urine 20-85%

clinical use

CMV retinitis induction 5mg/kg over 1 hr weekly x 2. Maintenance dose 5mg/kg I.V 1 hr once every 2 weeks.

Adverse effects

- dose dependent rephrotoxicity – the main
- neutropenia in 15%
- metabolic acidosis, fanconi's syndrome and decreased serum bicarbonate due to tubular damage.
- Dose limiting GIT intolerance

Interactions.

- avoid use with other nephrotoxic drugs.

FOSCARNET

-Phosphoformate

MOA

- Foscarnet is a potent inhibitor of the pyrophosphate binding site on polymerase where pyrophosphate exchange occurs during DNA replication
- inhibits DNA systhesis and cellular polymerases are also affected causing toxicity – renal dysfunction

P'KINETICS

- Not well absorbed orally
- usually I.V

- T1/2 = 3 HRS
- Excreted in urine

clinical use

- AIDs retinitis caused by CMV infections
- in extremely serious infections caused by HSV, HBV and HDV
- Acyclovir resistant Herpes infections
- resistant gancyclovir infections
- Activity against HIV ---not used because of it's toxicity

Adverse effects

- Renal impairment
- tremors, headache, fatigue, GIT symptoms (nausea, vomiting), genital ulceration,
- hypo and hypercalcemia
- Hypocalemia and hypomagnesemia
- anaemia and leukopenia ---less marrow toxic than gancyclovir
- Abnormal liver function tests

INTERACTIONS

-Adversely reacts with Aminoglycosides, amphotericin B, IDTA, pentamidine

Doses

- continuous infusion of 200mg/kg/day or 60mg/kg TOD
- Clinical use of forscanet is restricted to specialized units.

GAMMA GLOBULINS

- immune globulins
- obtained from plasma of normal individuals ands is out in most of the antibodies found in whole blood.
- Contains a variety of antibodies against specific viral antigens
- MOA- interferes with entry into cells by blocking penetration.

Clinical use

Administered parenterally

1. 1. I.M Injections of pooled gamma globulin 0.025-0.25 ml/kg during early incubation periods when it modifies progression of infections with hepatitis, measles, rabies, poliomyelitis and other viral infections. Protection lasts 2-3 weeks.
    - Doses can be repeated every 2-3 weeks for prolonged infections
2. special hyper immune globulins available for rabies, vaccine, varicella zoster, hepatitis B rhesis disease (rhesus iso immunization)
3. immune globulins can be use as adjuncts to other therapeutic functions.

Adverse effects

- Anaphylactoid reaction to foreign proteins- severe anaphylaxis

dose

- 100mg/kg for sandoglobulin given once a month.

INTERFERONS.

- enhanced production of these antiviral proteins is one of the bodies earliest responses to viral infections.

- All cells appear capable of producing them
- Several types:
  - alpha – produced by WBCs
  - Beta – produced by connective tissue fibroblasts
  - Gamma – produced by T lymphocytes
- all glycoproteins; each containing about 150 amino acids
- Peak within 24 hrs but start declining in 4 days.

MOA

- After attaching to cellular surface receptors, they initiate additional antiviral proteins production and stimulates macrophages to increase their oxidative metabolism
- thought to inhibit viral replication at 4 stages:
  - transcription
  - translation – protein synthesis
  - assembly and release
- physiologically regulate immune function by activating natural killer cells, cytotoxic T lymphocytes.

Clinical uses

- besides use in viral therapy, they are being tried for use in AIDs and cancer
- human tumors showing, some response include osteogenic sarcoma, multiple mycloma, melanoma, breast cancer, leukemias and lymphomas.
- 2 derivaties of alpha; 2a & 2b
  - have been used in hairy cell leukemia
  - have been used in conylomata accuminata (Human papilloma virus)
  - Chronic hepatitis B infections – alpha 2b.---usually in combination with ribavirin. Up to 40% pts will improve.
  - Chronic hepatitis C infections. Improvement in up to 50% - alpha 2b
  - interferon alpha – has been used to reverse chronic granulomatous dx e.g rheumatoid arthritis, sacordisis, connective tissue dx, systemic sclerosis e.t.c.
  - Rx and prevention of viral infections in immunosupressed and are used to prevent life threatening infections
  - HIV- known- lud mg o.d po. Infections of interferon given 3 days a week but sometimes daily. Optimal duration of therapy unknown. Most pts currently treated for 4-6 months.

Adverse effects

- are relatively well tolerated drugs
  - injections can cause a flu-like syndrome during first week of therapy – fever, headache, malaise, myalgia
  - High doses or chronic therapy has caused bone marrow suppression and neurotoxicity
  - Others
    - profound fatigue
    - severe weight loss
    - abnormal liver function tests
    - leukopenia
    - depression

- anorexia
- altered thyroid function test
- cardiotoxicity

AMANTADINE (Symmetrel)

- it's synthetic
- it's a tricyclic symmetric amine which inhibits uncoating of Influenza A, rubella and some tumor viruses, after they enter the host cells.
- Being a weeak base it buffers the PH of the endosomes, prevents acidification in the endosomes blocking fusion of the virus to the endosome thus prevents transfer to the membrane.
- It interacts with a protein located in the surface coat of influenza virus, inhibiting the coats thus stopping it's fusion to the membranes.
- Inhibition of imitation of infection and virus assembly is also by interferons with a protein located in the surface coat of the influenza virus.

P'KINETICS

- Amantadine is given orally, rapidly and completely absorbed with peak levels at 2-4 hrs.
- t1/2 20 hrs
- doesn't go significant hepatic metabolism most of the drugs 90% renal failure.
- Dose reduced in renal failure

Clinical use

- main use in prevention and rx of influenza A infection. 200mg/day 2-3 days before infection and continued for 6 days after infection---reduces incidence and severity of symptoms and magnitude of serologic response.
- 100mg/day for elderly.
- Epidemics – drug given for 6- 8 weeks.
- Other use : Parkinson's disease. Preps 100mg caps, 50mg 15ml syrups

adverse effects

- depression
- congestive cardiac failure
- orthostatic hypotension
- urinary retention
- psychosis
- dizziness
- insomnia
- nervousness, ataxia, slurred speech
- skin rashes
- provoke a massive release of catecholamines – arrhythmias

contraindications

- already established influenza
- children under 15 yrs
- other infections other than influenza

i**nteractions**

- avoid concomitant use of amantadine with anticholinergics, phenelzine, thiazides, trameterene
- caution in liver failure, kidney failure and pregnancy.

- the analogue of amantadine, Rimantadine works the same as amantadine. There's no dose

regulation in kidney failure

VIDARADINE (Vira A)

- adenine arabinoside
- least toxic and most effective purine analogue

Chemistry and MOA

- Vidaradine is a nucleoside analogue obtained from cultures of streptomyces antiboticus
- its phosphomylated to a triphosphate derivative in the cell, which inhibits viral DNA polymerase much more effectively than human DNA polymerase preventing DNA synthesis

Antiviral Activity

- has activity on, CMV, herpes simplex and herpes zoster, vaccinnia viruses, limited effect on most RNA and non herpes DNA viruses, Adeno virus

P'KINETICS

- Only administered topically as an aphthalmic onitment or as an I.V infusion
- has a limited solubility an so is not absorbed after ophthalmic application
- after I.V adminstration its rapidly metabolized to its main metabolite adenosyl hypoxanthine, which has some degree of antiviral activity.
- Widely distributed in tissues including CSF
- Excretion mainly in urine
- t1/2 – 4 hrs

Clinical uses

- herptic and vaccinal keratitis 3% ointment. Effective m ore on type 2 than type 2 herpes. Not effective on skin and mucous membs
- herpetic encephalitis and systemic herpes infections

Adverse effects

- GIT – anorexia, nausea, diarrhea
- rare – CNS – hallucinations, dizziness, ataxia, psychosis, atamia
- Topical preparations – lacrimation, burning sensation, irritation, pain and photophobia

Contraindications

- not given in pregnacy unless when the mothers' life is threatened
- monitor liver functions during therapy

RIBAVIRIN (Virazole)

-synthetic nucleoside analogue of guanosine phosphorylated by host cell enzymes. IT appears to interfer with synthesis of guanosine triphosphate, inhibit capping of viral mRNA and to inhibit viral RNA dependent polymerases

Antiviral action

- effective against RSV, HSV, Influenza A & B, parainfluenza, paramyxovirues, Lassa fever, HCV and HIV1

P'KINETICS

- Given orally and as an aerosol. - Oral bioavailability is 64%, increases with a high fat meal, decreased by antacids
- the aerosol has minimal systemic absorption, with respiratory fluids concentrations 100 times that in the plasma

- 50% metabolized to one major metabolite. 50% of drug metabolite appears in urine in 72 hrs.
- elimination primarily in urine
- half life 9.5 hrs, 40 days in RBCs

clinical use

- selected hospitalized infants and young children with RSV. Given as aerosol in oxygen tent or mask
- influenza A & B
- Lassa fever – the rx of choice as long as started early
- combination therapy in HBV

Adverse effects

- Decreased respiratory function in those with chronic respiratory dx
- dyspnea, chest soreness in those with compromised lung function
- rare – rash, conjuctivitis, anaemia
- teratogenic, embryotoxic in animals and mutagenic in mammals. No conception up to 6 months after drug.

IDOXURIDINE (stoxil)

- 5-iodo-2 deoxyuridine
- a water soluble iodinated derivative of deoxyuridine
- acts by introduction into viral DNA, unstable DNA formed with aberrant protein synthesis. Also inhibit pyrimidine formation and nucleotide interconversions.
- The active form, triphosphate, inhibits both viral and DNA sythesis.

Antiviral activity

- only active against DNA viruses
- herpes, varicella, vaccinia, polyoma virus and several others
- resistance commony develops after some time

P'KINETICS

- Given topically
- topical ophthalmic solution
- accidental oral intake, rapidly metabolized and excreted in urine

uses

- herpes simplex infections of eye. 0.1% solution and 0.5 onintment

adverse effects

- local irritation
- itching
- photophobia
- corneal clouding and small punctate in the corneal epithelium
- allergic reactions.

Read about

- oseltamavir
- zanamavir

ANTIRETROVIRALS THERAPY

Dr. E Omonge Friday, 18th June 2010

Objectives

- be familiar with the site of action of the various classees of ARVs
- understand components of HAART regimen
- ….

HIV VIRUS VIROLOGY

- Retrovirus- RNA virus with ability to change the RNA to DNA by using a reverse transcriptase enzyme
- Genome contains a gag-pol-env gene
- gp120- glycoprotein ---helps with attachment on the infected cells (CD4 receptor)
- gp 41- transmembrane protein – help in the movement of the viral cell membrane; attachment of gp 120 to the cell
- P 24- antigen for determining infections of HIV. Coat of genome/RNA. Makes the viral capsid
- Enzymes
  - reverse transcriptase – helps HIV virus convert its RNA to a ds DNA that infects/gets integrated into hosts DNA
  - intergrase – integrates viral DNA into the hosts genome.
  - Protease – cleaves off redundant parts of the DNA formed forming a mature virion.

Replications and Pathogenesis

- CD4 receptors are the binding sites---virus uses gp 120 ----viral attachment.
- Chemokines helps with the attachment; co receptors. They allow for viral integration into the cell; CXCR4 & CCR5. Virus membrane emerges the host cell's.
- The RNA in the capsid undergoes reverse transcriptase and the new ds DNA is intergrated into the host cell genome forming a provirus that has a capacity to form more viruses.
- Viral replication takes place with the activation and control by enzymes such as proteases to produce mature daughter viruses= regulatory proteins

Prevention and control

- abstinence
- faithful partners
- condoms

DRUG ACTION SITES

- Drugs inhibiting entry
  - Attachment inhibitors
  - chemokine co-receptor antagonists
  - fusion inhibitors
- Reverse transcription inhibitors
  - prevention of change of viral RNA into DNA. 2 types of reverse transcriptase inhibitors:
    - Nucleoside RTI
    - nucleoside RTI
    - Non-Nucleotide RTI
- Integrase inhibitors.

- Inhibit viral DNA integration into the genome DNA
- Protease inhibitors
  - prevent cleaving of viral info into functional viral components
- maturation inhibitors – prevent viral maturation

NUCLEOSIDE ANALOGUES RTIs

- first antiretrovirals drugs introduced
- are dideoxynucleoside analogues which are phosphorylated into the active triphosphate form
- the triphosphate metabolite competitively inhibits the reverse transcriptase by acting as an alternative substrate for the enzyme
- once the metabolite is incorporated into the developing DNA strand, chain termination ensues.
- AZT (azidothymine) replaces thymine and terminates chain.

NNRTIs

- binds at catalytic enzyme site of the reverse transcriptase enzyme and inhibits its activity.

Protease inhibitors

- inhibit the protease enzyme
  - prevents viral proteins from becoming functional
- most mimic peptic bonds
  - look like proteins to the protease enzymes
  - they compete with natural substrates.

Fusion inhibitors

- prevents fusion of viral envelope with cell membrane
- prevent entry of viral RNA and proteins into cell

ANTIRETROVIRALS AGENTS

NRTI

- Zidovudine (AZT, ZDV)
- Didanosine (ddl)
- zalcitabine (ddc)
- stavudine (D4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine(FTC)

NNRTIs

- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- Etravirene
- rilprivirine

Nucleotide analogues

- tenofovir (viread)

PI

- Saquinavir
- ritonavir
- indinavir
- nelfinavir

- amprenavir
- lopinavir/ritonavir
- atazanavir
- fosamprenavir
- tprinavir
- darunavir

Fusion inhibitors

- enfuvirtide (T-20)

ZIDOVUDIINE (AZT, ZDV, Retrovir)

- Thymidine analog. Requires phosphorylation to triphosphate form
- additive or synergisitic with most NRTIs, NNRTIs and Pis in vitro
- antagonistic in vitro with stavudine (d4t)
- Evolution of dosage regimens: 200mg q4th => 100mg 5x/day => 200 mg TID => 300 mg BID
- Plasma t1/2 – 1 – 2 hrs, intracellular t1/2 – 3 to 6 hrs
- CSF : plasma ratio = 0.6
- dosage adjustments necessary in renal dysfunction

EFFICANCY AS MONOTHERAPY

- 1st agent to show survival benefits in AIDS pts
- potential benefit in AIDS-dementia complex and HIV associated thrombocytopenia
- effective in prevention of periantal transmission and in PEP- post exposure prophylaxis

Utility in 2001

- uses as part of HAART regimen
- monotherapy only in pregnancy if HAART is not indicated

ZDV – Specific toxicities

- bone marrow suppression (anaemia, neutropenia)
- dose related, synergistic toxicities with other drugs such as TMP-SMX, ganciclovir, e.tc
- headache, nausea, vomiting, and myopathy, nail changes
- Hepatotoxicity, fever, rash---rare

Resistance

- develops after several months of therapy.

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