



Microbiology

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Virology – Antivirals 1

JU- 2nd Year Medical Students

By

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Antivirals

- Anti herpes
- Anti CMV
- Anti influenza
- Ribavirin: RSV, influenza...
- Anti HIV, HBV and HCV
- Interferons

- Vaccines kept under control and eradicated some viral infection such as MMR and smallpox
- But for no vaccine many viruses, therefore antivirals are needed
- More than 30 antivirals are available, but majority have narrow spectrum

❑ Antivirals discovered by:

- Random screening
- x-ray crystallography:

determines the 3 D structure of viral proteins then design inhibitors for such active proteins e.g NA
Inhibitors bind to the active site of viral NA but not human or bacterial NA.

✓ Selective toxicity

Site of action for antivirals:

1 – binding to the free virus particle:

- Stabilizing the virus by crosslinking its structural proteins and inhibiting release viral genome

2 – interference with virus attachment:

- Synthetic receptors acting as decoys and preventing infection
- e.g soluble CD4 for HIV
- HIV fusion inhibitors (**enfuvirtide** binds gp41 (of HIV And prevents HIV-CELL fusion

3 – Inhibition of viral uncoating and nucleic acid release:

- e.g Amantadine blocks M2 channels in influenza virus and prevents uncoating

4 – Inhibition of viral nucleic acid transcription and translation

- Inhibiting viral enzymes such as:
- Influenza RNA polymerase (transcriptase),
- herpes thymidine kinase and DNA polymerase
- HIV RT, Integrase and protease

5 – Interference with cellular processing of viral polypeptides:

- e.g acylation and sugar addition but no selectivity
- the least good approach since cellular and viral proteins are processed in similar way

6 - interference with budding and virus maturation

- e.g NA inhibitors : inhibit influenza release from cells
- HIV protease inhibitors: inhibits maturation, immediately after release and during maturation

- **Usage:**

- 1- Therapy:

- Commonest
- As early as possible, on appearance of early signs , within 24 hours or usually effectiveness will decrease
- e.g acyclovir for cold sores and amantadine for influenza

2- prophylaxis:

- less common
- ❖ e.g: acyclovir for recurrent genital herpes
- Acyclovir has short half life and frequent dosing is needed (5 times a day)
- Penciclovir (same spectrum of aciclovir) has longer half time and can be given 3 times a day
- ❖ anti influenza drugs
- ✓ advantages over vaccines:
 - act faster e.g within an hour
- ✓ Disadvantage:
 - Once stopped the patient becomes susceptible to infection

☐ Pregnancy:

- Contraindication
- Exception is HIV mother where **zidovudine** and lamivudine can be used to decrease the risk of fetus infection

- **Prodrugs:**
- chemical side groups attached to the active antiviral molecule to enhance adsorption and tissue penetration
- Host enzymes then cleave off the side chain from the prodrug
- release concentrations of the active drug that are often higher than when active drug given directly
- ✓ famciclovir (a diacetyl prodrug of penciclovir):
- ✓ valaciclovir, (prodrug of Aciclovir)

❑ valaciclovir, (prodrug of ACV):

- absorbed from the gastrointestinal tract and converted to ACV in the intestine and liver.
- Approximately 60 per cent of the prodrug given by mouth is absorbed, compared with 20 per cent absorption of ACV.

❑ famciclovir (a diacetyl prodrug of penciclovir):

- Hydrolysis in the intestinal wall
- metabolism in the liver
- removal of both acetyl groups,
- oxidation of this deacylated form converts famciclovir to penciclovir

- **Aciclovir and related compounds:**

1 - ACV and penciclovir possess an excellent combination of biochemical and pharmaceutical properties

- anti-herpesvirus specific

- **Mode of action**
- **Aciclovir (guanosine analogue):**
- First, aciclovir phosphorylated to the monophosphate by **herpesvirus TK** i.e only in herpes-infected cells (cannot be achieved by normal cellular TK)
- i.e low toxicity as its tissue distribution is limited to virus-infected cells
- The viral TK is less 'precise' than the cellular TK and will accept 'fraudulent' substrates such as ACV.
- Once ACV is phosphorylated in the cell it cannot emerge because of the charged phosphate group that has been added by the TK enzyme.

- In addition, when the pool of 'normal' unphosphorylated ACV in the cell is depleted, more ACV molecules move across the plasma membrane and these are in turn phosphorylated.
- the drug accumulates only in virus-infected cells.
- Phosphorylation to the di- and triphosphate is then achieved by cellular enzymes

- The triphosphated active drug, binds to and specifically **inhibits the herpesvirus DNA polymerase**. (It has little effect on cellular DNA polymerase and hence is not Toxic and considered clinically safe
- for example, patients with recurrent herpes simplex have been effectively treated with daily doses for many years without side-effects.
- BUT A latently infected cell cannot be cleared of herpesvirus by ACV i.e No eradication of latency

- **Penciclovir,**
- has a similar mode of action of ACV
- its clinical effect is similar
- Kept more tightly within the cell as the given less often.
- one-hundredth the potency of ACV in inhibiting herpesvirus DNA polymerase
- but as it accumulates in very high concentrations and has an extended half-life therefore given less frequently

- Usage:
- ✓ Treatment:
 - Treating herpes simplex encephalitis, if administered early.
 - Treatment of severe VZV infections in the elderly and in immunocompromised patients (higher doses required than those for herpes simplex infections)
- ✓ Prophylaxis:
 - Herpes simplex and zoster infections in bone marrow and heart transplant patients.
 - Prevent the spread of virus in those already infected.
 - Continuous treatment to prevents recurrent HSV-1 and -2 infections, particularly those of the genital tract

- **Anti CMV:**
- Ganciclovir: acyclovir derivative
- Cidavir: nucleoside analogue

- **Foscarnet:**
- It blocks the pyrophosphate binding site on herpes DNA polymerase
- Toxic to kidneys and bone so its usage is limited to life threatening cases that are resistant to aciclovir

- Anti-influenza:
- **1 Amantadine and rimantadine**
- **Mode of action**
- One of the M2 structural proteins of the influenza virus acts as an ion channel across the viral membrane
- allows passage of hydrogen ions to the interior of the virus within the endosome
- under this acidity change, the two virus core proteins, NP and M, which bind closely with the viral RNA, will dissociate to allow the viral RNA to enter the nucleus to replicate.

- **Amantadine and rimantadine:**
- Blockage of the M2 ion channel which stops the induction of low pH
- leads to inhibition of all subsequent events that would normally lead to infection.

- **Clinical application**
- Treatment of influenza A
- prevent influenza A in 80 per cent of individuals:
- The antifu drugs may be used prophylactically when the presence of influenza A virus in the community is confirmed.
- Prophylactic use can continue for 5 weeks or until the end of the epidemic
- prophylaxis is recommended only for the 'special risk groups':
- the over-75s, diabetics, persons with chronic heart or chest diseases who have not been immunized or who wish to receive extra protection.

- **2 Inhibitors of influenza neuraminidase (NIs)**
- .(**oseltomivir** and zanamivir)
- NA normally acts at the stage of virus release from the cell
- inhibition of the enzyme causes virus particles to aggregate at the cell surface THUS the virus will not be released to infect adjacent cells.
- These antivirals are effective against influenza A and B Viruses
- Used to prevent infection and reduce symptoms in persons already infected.

- The NIs are already overtaking M2 blockers as the drugs of choice against influenza
- The NIs can be used but must be given quickly, within 24 hours of onset.
- Very useful for new pandemics of influenza A virus, when no vaccines would be available for the first waves of infection

- **3 Ribavirin:**
- nucleoside analogue
- has antiviral effects in cell culture.
- Poor selectivity as it inhibits cellular dehydrogenase rather than any important viral enzyme.
- used to treat a wide range of viruses including:
 - 1 influenza.
 - 2 It is licensed in several countries for use as an aerosolized drug in children seriously ill with RSV.
 - 3 Lassa fever
 - 4 hantavirus infections,
 - 5 in combination with IFN, to treat hepatitis C.

- **Side effects:**
- ✓ Acyclovir (antiherpes):
 - is very safe but has GIT side effects
 - Care with abnormal kidney functions, renal failure (70% of acyclovir excreted unchanged in urine)
- ✓ Ganciclovir (anti CMV):
 - Neutropenia in 1/3 of patients
 - Less common; thrombocytopenia, rash and nausea
- ✓ Amantadine(anti influenza A):
 - Neuro effects as jitteriness, disappear on stopping the medication

END