University of Jordan
Faculty of Medicine

Medical Committee
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Introduction to

Microbiology

Title :

Anti-viral drugs

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: 28

- ○ Slides
- ○ Handout
- ● Sheet

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Anti-viral drugs

{Please read these notes together with the slides since I only wrote what the doctor added}

Apologies in advance for any mistakes

In this sheet we are going to talk about anti-viral drugs, we are going to talk about certain groups or anti-viral drugs which target certain steps of the virus cycle, such as:

-herpes virus, hepatitis virus, herpesviridae as a family because it has a large number of viruses, they are eight genuses.

We have six hepatitis viruses, we have the HIV, we are going to talk about the viruses which cause the upper respiratory tract infections.

Slide #2:

*viruses have no cell wall and made up of nucleic acid components.

*viruses containing envelope and to be specific these viral proteins are antigenic in nature.

*viruses are obligate intracellular parasite:

→ they leave the living cell in order to multiply and only the replicated or multiplying viruses are inhibited by anti-viral drugs.

*they do have a metabolic machinery of their own..they use the host enzymes:

→ they use their host enzymes that are partially complete, true for DNA viruses because we said that certain DNA viruses are totally or partially dependent on cellular enzymes, the RNA viruses produce by their own enzymes BUT still most of the viruses are dependent on the cellular machinery or organelles in order to synthesize proteins.

slide #3

*certain viruses are multiply in the cytoplasm and others do in the nucleus (we talked about that previously).

* most multiplication take place before diagnosis is made (important point):

→ this is important point in talking about anti-viral drugs, SO once you reach the diagnosis, the virus that infected the cell and multiply inside the cell, once the patient is symptomatic (once the patient is symptomatic; the virus is multiplied and the body start to produce antibodies against the virus) ---> at this stage, in reality, for acute viruses infections, such as: upper respiratory tract infections, there is NO need to treat the patient with anti-viral drug, because it is an acute illness which lasts for 5-7 days and then is going to resolve completely without any complications.

If you need to treat the infection with anti-viral drug, you should treat as early as possible, to get the maximum effect of the anti-viral drug.

In healthy individuals, the body's defense system is more than enough to clear the virus in 5-7 days. BUT in those of immunocompromised, there is one of the systems or factors or the defense mechanisms deficiency, the anti-viral drugs are very helpful in order to clear the

virus and in most of the times you can also minimize the symptoms in case of chronic viral infections.

Slide #4:

(I will just mention the addition informations that were mentioned by the doctor, so please refer the slides ☺)

Many antiviral drugs are purines or pyremidines analogues.

The second point: many anti-viral drugs are prodrugs; they are inactive, they require activation, they are activated by either the viral enzymes or the cellular enzymes.

QUESTION:

Which is better for us, the activation by viral or cellular enzymes?

→ by viral enzymes; it will target the infected cell only and will spare healthy cells, SO even if it is enter into the non-infected cell it will not be activated, BUT once it enters into an infected cell, the presence of this viral enzyme is going to be activated and it will affect the cell.

QUESTION:

What do we mean when we say purine analogue, or what is the mechanism of blockage?

→ It mimics the nucleotide but in fact it is not a nucleotide…

(((remember: when we talked about the tautomeric mutations, that are in a way similar but differ in the bonding and these stuff, this is in the an away similar to that, SO after it is activated, it is incorporated into the new chain of the RNA or the DNA, but once it is there it

requires bonding to attach the next nucleotide, it is not a nucleotide so it blocks the synthesis once it is inserted, the replication or the elongation of the RNA or the DNA does not take place)))

Many antiviral drugs need to be phosphorylated by viral or cellular enzymes in order for them to be active.

The third point: anti-viral agents inhibit active replication so the viral growth resumes after drug removal:

→ We said that replicating viruses are affected by the anti-viral drugs BUT the latent or dormant viruses are not.

**the viral replication resumes after drug removal: once you prescribe an anti-viral drug to a patient you have to ask him not to stop if even if he feels improvement because the replication of the virus was contained to an extent; stopping of the drug would expose the virus to a sub-optimal concentration of the drug. The drug will not be effective against the virus. Moreover, this will produce a compensatory mutation in the virus, and the virus will become resistant to the antiviral drug even if you give it at the right concentration.

There are three defense mechanisms against viruses:

1) Cellular
2) Humeral
3) Anti-viral drugs

Slide #5:

Point number 3:

Clinical efficacy depends on achieving inhibitory concentration at the site of infection within the infected cells:

→ the conc. Of the drug at the site of infection should be an effective dosage in order to inhibit the replication of the virus.

Slide #6:

We talked about the different stages in the viral replication (adsorption, penetration, uncoating, transcription, translation, replication, assembly, and release), each of which is inhibited by certain anti-viral drug.

Slide #7:

(look at the figure in the slide please ☺)

*for the virus entery and penetration we have two drugs which target the HIV virus :-

1- the infuvirtide or fuson (الاسم التجاري).

2- the maravoric which is the CCR5 receptor antagonist.

***the CCR5 receptors: the coreceptor require for the virus entry

*for uncoting we have a drug called amantadine (for influenza A virus)

*for early protein expression we have fomivirsen which target cytomegalo virus.

* the nucleic acid synthesis, most of the drugs work on this area, we have purine, pyrimidine analogues and reverse transcriptase inhibitors; these work on preventing or blocking the replication of the viral genome. Protein synthesis and processing (protease inhibitors)…

inhibits cutting the protein into smaller polypeptide chains. The release of the viruses is inhibited by neuroaminidase inhibitors, like influenza A antiviral drugs.

Slide #8:

We will start with drugs that work on herpes viridae, we will talk about (acyclovir, valacyclovir, famciclovir and penciclovir) as a whole family, after that we will talk about (ganciclovir, cidofovir and foscarent) as individual drugs.

Slide #9:

What is the difference between acyclovir and valacyclovir..and the difference between famciclovir (can be administred orally) and penciclovir?

→after activation or phosphorylation in fact, they are the same BUT the difference is in the bioavailability of the drugs. Better bioavailability means a higher concentration of the drug thus we can give a lower dose concentration of the drug.

Slide #10: the doctor did not mention any thing out of the slide.

Slide #11:

<u>The first point</u>: viral thymidine kinase (activator) converts the drug into monophosphate form after that the ((cellular enzymes)) transform it to

the di and tri phosphate which is the active form, which is by the viral DNA polymerase when become incorporated in the growing DNA chain and block the elongation of the chain.

Slide #12: the explanation of the figure is the same of the previous paragraph.

Slide #13:

*uninfected cells do not phosphorylate acyclovir:

→ Because thymidine kinase will be only present in the infected cells and the drug will be only active in the infected cells.

Slide #14:

This slide talks about the spectrum of anti-viral drugs.

{ the doctor does not ask us to know everything about each drug but we will talk about the most important and we must know and memorize them }

For the HSV, the drug of choice is acyclovir..

Ganicyclovir is the drug of choice for cytomegalovirus

Slide #15:

He read the slide, but he said some comments about the first and the last points:

**oral bioavailability: what is the difference when we say that it is 90% or 5% or anything else?

→ it means that it is not an effective route of administration if it is low. If the oral route bioavailability is higher, you can administer the drug orally.

And about the last point: we must know it because when we are sitting in a clinic we have to know all the forms of drug available.

Slide #16:

This slide is important and it talks about the side effects of (acyclovir-ganiciclovir):

The GI symptoms:

-- nausea, vomiting and diarrhea.

-- nephrotoxicity: crystalluria, haematuria and renal insufficiency.

-- myelosuppression: neutropenia (penia means drop or decrease) and thrombocytopenia especially with ganciclovir.

(thrombocytopenia (anemia) the decrease in the number or RBCs and it is the same of anemia).

** MYELOSUPPRESSION: effection of the bone marrow, it affects the origin of the immune cells.

(there is a question the doctor asked it and said we have to look for it)

**the question is:

These drugs are prodrugs and they are activated by cells that infected by the herpes virus by the presence of thymidine kinase, SO how do they affect or cause myelosuppression?

Slide #17:

Therapeutic uses of anti-viral drugs:

Acyclovir: it can be used in all forms of HSV also in encephalitis.

HSV (herpes simplex virus) we have:

1) Type one: we call it “infection above the ways” and it infects the oral and mucosal cavity infections and it can also by secondary viremia infect the CNS.
2) Type two: we call it “below the ways” and it can infect the genitalia.

   Ganciclovir is the drug of choice for:

   - CMV retinitis in immunocompromised patient.
   - Prevention of CMV disease in transplant patient.

NOTE: most of the times the CMV only infects the immunocompromised patients either as a result of illnesses such as HIV or due to drugs which suppress the immune system such as in transplant patients, we must introduce a drug in the case of CMV infection because the immune system cannot control the infection.

Slide #18:

The third point : cidofovir is an active drug and does not require phosphorylation, but since it does not require any phosphorylation, it would also inhibit the DNA synthesis of the non-infected cells, so the side effects are high BUT most of the effects are directed to the virus because it reproduces faster than the cell. It

**it is available for IV, intravetreal injection (in the eye), and topical.

Nephrotoxicity is a major disadvantage

Slide #19 and #20: the doctor did not mention anything other than what is mentioned in the slides but said that:

The only available form of the vidarabine is ophthalmic ointment.
Adenosine analogue

** its use is limited to HSV keratitis only (keratitis: is inflammation of the cornea).

The only available form is ophthalmic ointment.

It has a low bioavailability (2%)

Slide #21 and #22: the doctor did not mention anything other than what is mentioned in the slides.

ADH (antidiuretic hormone): the hormone that blocks urine excretion

NOTE: we have two active drugs (they do not require activation or phosphorylation) :

1- **Foscarnet.(alternative for acyclovir in case of acyclovir resistance. Or replacement for ganociclovir in case of resistance)**
2- **Cidofovir.**

By the slide #24 we finish talking about all the herpes virus..we are going to talk about the viruses that cause the respiratory tract infections…. Although the mechanism of action for these drugs (aforementioned) can cover most of the viruses they are usually administered only for the above mentioned diseases.

Slide #25:

We are going to talk about the influenza treatment:

- Amantadine/ rimantadine (for influenza A)
- Oseltamivir/ zanamavir (for influenza A and B)
- Repatidin for RSV

(neuraminidase inhibitors):
In influenza we have two glycoproteins or spikes:
1- Hemaglutannin (H)
2- Neyramin (N)

--one of their functions is: upon the budding of the virus, the virus remains attached by the (N) to the receptors of the cell. It requires cleavage after that the virus is released, SO if you block this step you prevent the release of the virus.

Slide #26:

the doctor only added the following sentence to the second note:

--protein M2 is unique for influenza A and does not present in influenza B. this is why the first two drugs are unique to influenza A virus

Slide #27 -- #29: the doctor only read the slide.

But know that BBB stands for blood brain barrier.

Slide #30:

The third point: prophylaxis means preventive before the development of the symptoms of the disease, when we talk about prophylaxis we talk about vaccines.

QUESTION: how can we use prophylaxis in acute infection?

Answer: If all the inhabitants of one house are infected except one of them, we can treat him to keep him from the infection.

Slide #31: the doctor read the slide.

Slide #32:

It talks about the pharmacology of ribavirin:

* it blocks the synthesis of RNA.

When we use it against hepatitis C it should be associated with the use of interferon.

Note: it is used also for treatment of RSV which is responsible for acute bronchitis and bronchopneumonia in infants below one year age.

Slides #33 and #34: the doctor only read the slides.

Slide #35:

When we say anti-viral drugs for hepatitis we mean hepatitis B and C.

We have six types of hepatitis:

A and E are acute hepatitis.

Hepatitis D is associated with B so when B is inhibited D will be inhibited.

Hepatitis G is a newly discovered virus and it is associated with hepatitis C.

NOTE: pegylated interferon means slow release interferon.

Slide #36:

This is a figure of the Human Immunodeficiency Virus.
We learnt about its way of replication previously, notice the two copies of +ssRNA. It is a reverse transcribing virus.

Slide #37: these medications work in different ways to reduce the viral road, as we mentioned before each of these drugs acts on different step in the viral reproducrive cycle. (go back to the replication cycle of HIV!)

Slide #38:

The only information that not written in the slide is the difference between nucleoside and nucleotide:-

-nucleotide: are the nitrogenous bases
-Nucleocide: phosphorylated nucleotides
{ these names are not for memorizing but you should at least know one or two of them..they share the last few letters }

Slide #39: the doctor only read the slide.

Slides #40 - #43: the doctor said they are NOT important.

Slides #44-#48

: the doctor only read the slides