Medical Committee
The University of Jordan

# PHARMACOLOGY

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SHEET

SLIDES

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# ANTI-VIRAL DRUGS

## Treatment of influenza:

we had 4 drugs to treat influenza (in the past), however now we only use 2 drugs, the old drugs (attachment inhibitors ) are amantadine and rimantadine both are no longer used for influenza treatment , amantadine is used for treatment of Parkinson we will take this later. We are interested in **neuraminidase inhibitors** (the other drugs) oseltamivir (tamiflu) and zanamavir (relenza) these drugs block viral **neuraminidases** that are responsible for catalyzing the cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids a necessary process for viral release from host cell surface. And thus they prevent the release of virus from infected cell.

When you look up these drugs you will find out that these drugs are useful for combating influenza infections:

zanamivir: by inhalation , oseltamivir: taken orally

what you won't find in books is **when** are these drugs actually used, being the only drugs active against influenza right now so guidelines are set for their use.

mechanism of action is by inhibiting the spread of the virus/infection, so these drugs have to be used within 48 hours of the development of sign and symptoms of influenza as recommended by doctors, otherwise as after 48-72 hours, the number of virions will be very high (very high level of viral spread) and the drug will not be active.

So those drugs are used for inhibiting signs and symptoms of influenza within 48 hours after appearance of symptoms.

The main use for these drugs (zanamivir & oseltamivir) is **prophylaxis** of influenza for immunocompromised patients.

So when these drugs are administered, it is crucial to be within 48 hours because the virus replication is highest between 24-72 hours after onset of illness , from the slide: when a 5day course of therapy is initiated within 36-48 hours after the onset of symptoms, the duration of the illness is decreased by 1-2 days compared with patients taking placebo. So we only decrease the duration of infection rather than actually killing the virus and treating the symptoms so we must be sure that the benefit

is more than the risk , the risk here being the development of resistance so we shouldn't overuse these drugs.

these drugs decrease the severity of the disease and the incidence of secondary complications in children and adults. influenza can cause serious complications in children under 1 year of age or children (even more than 1 year) but with concomitant problem like asthma.

once-daily prophylactic effect is 70-90% preventing disease after exposure , same idea as acyclovir the patient is immunocompromised so we give him acyclovir for prophylaxis of h.influenza or Tamiflu (oseltamivir ) for prophylaxis of influenza.

**again giving a treatment for viral infection is not a cureness totally, it will be a reduction of the duration of infection, so we always need to balance the risk and benefit.**

important issue: after the outbreak of H1N1 virus in 2012, oseltamivir was active against 100% of infuenza viruses now its affective against 97%, this will not stop even here in Jordan. (so 3% of influenza visuses are resistant to oseltamivir)

oseltamivir is taken orally while zanamivir is inhaled , simply its easier to take the oral type especially with children so oseltamivir is the drug of choice even though resistance against it is developing ( we should keep an eye on that), oseltamivir doesn't cause toxicity but it does cause vomiting and nausea, the serious side effects are caused by zanamavir which causes exacerbation of reactive airway disease like in asthma patients so its contraindicated with patients with **chronic obstructive pulmonary diseases COPD** (asthma, bronchitis, emphysema). Asthma and bronchitis are related with smoking causing the patients to breath heavily). zanamavir causes allergy like problems with these patients.

the bottom line is with treating influenza we lost activity of attachment inhibitors (Amantadine and Rimantedine) ,we still have neuraminidase inhibitors affecting most of the viruses, this group contains 2 drugs; oral type oseltamivir and inhaled type zanamavir (needed with patients infected with oseltamivir resistant viruses).

**respiratory syncytial virus** this is an odd one ,**RSV** this virus causes respiratory problems like bronchiolitis. we don't really treat it because it resolves alone without complications normally however in risk patients like children with asthma and elderly so we are forced to use **ribavirin** which is not even approved by the FDA , the efficacy is not established,

we shouldn't prescribe this drug. It's used in Russia, brazil but not here, however this drug is used in other cases :

its an antimetabolite that inhibits influenza RNA polymerase non-competitively in vitro but poorly in vivo (the drug is weak). An aerosol form is used against RSV ,adverse effects include anemia due to hemolysis and bone marrow suppression, now if we are asked what is the drug of choice for RSV ? no drug is available although in some countries ribavirin is used but it's not approved by the FDA.

**Oseltamivir and Zanamivir are the last drugs resorted.

## AIDS:

we will discuss many things here in Jordan only 589 cases only, and 400 cases of these are not Jordanian. So our culture is protecting us from this disease.

history of AIDS tells us that the real name of the disease is Gay-related immune deficiency GRID, the first cases where discovered in the gay community in Texas and not from monkey's then why is it called AIDS while apparently the gay community didn't like the name . now, how did it affect women? it was transferred through contaminated needles (heroin), blood transfusions.

The problem is this disease that its unbelievably complicated and you cant really cure the patients the only way to stop it is by banishing all patients that HIV positive because it can also be transferred vertical (from a mother to her child), in sub-Saharan Africa the situation is horrible and in the united states the number of AIDS patients is huge , fortunately its not common in our countries.

AIDS what is unique about it ? **integrase/integration** combining its genetic material with the chromosomal DNA which is very bad , when the virus infects the cell it first attaches itself to it (fusion) then it releases its RNA, RT(reverse transcriptase) turns it to DNA and it's double stranded, this is integrated with the chromosomal DNA in immune cells especially **memory cells** and wont get out. how we measure it? CDA, CD4 (not required).

AIDS is targeted in all the infection steps fusion, transcription integration, cleavage, release. so many drugs are available; anti-fusion, anti-release, anti-integrase, anti-transcription drugs, anti-packaging and budding ..... yet we cant treat it we only cover it and prolong the patient's life at most 10-15 years .

## HIV positive VS AIDS patient

HIV positive : patients have the virus but the real effect wont start until 10-15 years while AIDS is the ongoing disease. (a latent period till the patient has symptoms). So HIV positive means that he has the virus but symptoms have not developed yet. AIDS patient has symptoms.

the main problem in treatment is that the virus keeps on **mutating** against the drug given , that's why we never use one drug to treat AIDS , we use multiple regimen that have different mechanisms of action , anti-fusion drugs, that inhibit integration, anti protease to inhibit the spread out …...

student Question: we cant really cure the patients the patient will die eventually so why not ease his death and make it fast ? well this is really complicated as the issue here is that we cant really put a price on life or decide whether someone should die or not most people want to prolong their life as much as possible , an example clivant prolongs life of cancer patients for 10 years while another drug has only been approved because it prolongs the patients life 6 mouths only, its also very expensive (1000 JD monthly), It's used in Jordan but the patient will pay the cost. This matter is to keep the patient alive.

AIDS Drugs :

hints will be given

oldest drug is **Zidovudin** which is an antimetabolite block metabolite, this drug is toxic because it has **no selectivity** causing bone marrow problems like anemia , leukopenia ,however the patients must take it to the limit that he can tolerate it, the bigger problem is that this immunocompromised patient immunity is getting even worse .

Azidothymidine (Zidovudin) is a potent antagonist of reverse transcriptase it's a chain terminator , cellular enzyme phosphorylate AZT to triphosphate from which **inhibits RT** causing the chain termination ,this drug is only used for AIDS.

another drug is **Didanosine** its just like Zidovudin; an antimetabolite same effects and side effects, and it inhibits RT by antimetabolite mechanism.

****Antimetabolites cause bone marrow suppression** (except acyclovir)

## NNRTI:

Another mechanism to attack RT rather than to be antimetabolite is to directly inhibit RT (just like Foscarnet). This is done to decrease the resistance or to decrease the rate of mutations against the drugs. so we always treat aids with many action mechanisms the drug we need to know is **Nevirapine** it's a non-nucleotide RT inhibitor (NNRTI).

the problem with these drugs NNRTI or nevirapine is they develop a rash in 20% of patients, so to reduce this problem we start with a low dose and increase it with time as the patient's body adjusts/tolerates to it (**escalation** of the dose) . over 14 days providing better tolerance and less rash , sometimes the rash can be strong and severe but this isnt the case here.

another problem is psychiatric; CNS problems, sedation, insomnia, wild dreams ,dizziness, confusion, feeling of disengagement , the AIDS patient already has this but again we talk about risk vs benefit take it or die .

rash occurs in up to 20% of patients, usually in the first 4-6 weeks of therapy. Although typically mild and self-limited, rash is dose limiting In about 7% of patients . women appear to have an increased incidence of the rash , so the drug is escalated.

## Another mechanism : inhibition of protease

-The virus uses the machinery of the cell to synthesize viral polyproteins which are cleaved by protease into number of essential enzymes. So by inhibiting protease >> inhibition of replication.

best discovery, this one made a difference, this drug inhibit the replication in general, the pervious drugs (NNRTI) didn't make much of the difference because work to inhibit RT, so we need a new strategy now that affect another thing rather than affecting reverse transcriptase.

Examples of these drugs : **saquinavir & ritonavir**

**they are orally active , side effects include GIT irritations and hyperglycemia , and they interact with cytochrome P450.** this is very important.

they interact and inhibit cytochrome P450 so you need to be very careful and think very well before prescribing other drugs, very serious problems can happen .

a trade mark for these drugs is buffalo hump (formation of huge hump), like in corticosteroids.

## Highly Active Anti-Retroviral Therapy:

there is no cure for AIDS, most of cancers, diabetes, hypertension most cases of asthma and many disease we just treat the problems or prevent more damage … however the problem with AIDS and cancer the patient life is really short and we need to silence the symptoms how?

combination therapy (drug cocktails) HAART, are very effective and can reduce viral load level in the patient below detectable levels implying that HIV replication has ceased. examples:

1. NNRTI-based regimens (1NNRTI +2NNRTI)
2. PI-based regimens (1 or 2 PI(protease inhibitors)+ 2 NTRI (nucleotide reverse transcriptase inhibitor)

   **PI is better than NNRTI

these combinations are very effective; however, the problem of these complicated regimens is COMPLIANCE. And the components of HAART MUST be taken at different times. Compliance (meaning the patients won't take these drugs because of their side effects so you need to explain to the patient that this is the only way and that he needs to take these drugs as planned. Because if the drugs ( PI) aren't taken for 1-2 days, resistance will develop causing more problems. very fast manipulation causing the resistance.

non-compliance with protease inhibitor therapy is of serious concern as the new virus that emerges is resistant to the inhibitor being taken and also resistant to other protease inhibitors. If the patient develops resistance against one protease inhibitor, it will develop against all other protease inhibitors and those therapies (which are invented in 1995) won't work .

other drugs and combinations but aren't required now

A new good AIDS drug is **Raltegravir** just approved to be added to HAART regimen, the doctor says it was approved in 2012 , but it was approved by FDA in 2007 and for children in 2011. This is an integrase inhibitor , targeting HIV integrase that integrates the viral genetic material into human chromosome, it could be added to HAART combinations

there are 2 more drugs that we wont be asked about but we need to understand the situation

Enfuviride is a peptide derived from gp41(P-glycoprotein 41) can inhibit infection, probably by blocking the interaction of gp41 with cell membrane during fusion.

## Hepatitis B and C

both are infections within liver. hepatitis c **must be treated**, the drug of choice is interferon Alfa with ribavirin (an antimetabolite that is not approved for influenza infections but used in some counties)

Interferon Alfa:

we have in our bodies interferons Alfa and beta and gamma

we use Alfa for hepatitis , from slide : endogenous proteins induce host cell enzymes that inhibit viral rna translation and cause degradation of viral mRNA and tRNA , meaning they are endogenous antivirals.

interferons are given as injections , they inhibit everything generally. from slide: binding to membrane receptors on cell surface, may also inhibit viral penetration, uncoating , mRNA synthesis and translation ,and virion assembly and release .

the first non-selective antiviral drugs are interferons (alpha and beta), they inhibit all viral infections (HSV,CMV, HBV, even we can use them in AIDS) however, this is not approved and we don't use them for all infections many reasons that we will not mention and not required.

We don't use it as interferon itself, we add something called **pegylated** interferon Alfa ; *sustained* drug release (just like benzathine penicillin which we took before- colloides)

instead of giving the injections daily we give them weekly by pegylating them that insure sustained release (it's given intramuscular). This is applied to the treatment of hepatitis C and it's long (24-48 weeks) depending on severity could be more than 1 year , (pegylated interferon Alfa + ribavirin ) , we can know when the patient is cured by measuring the markers of the infection. (we can use the non pegylated interferon alpha if the patient wants that and put up with daily injection!)

usually we don't treat hepatitis B unless the patient is immunocompromised ….. pathological conditions or if the patients

want to , we use drugs to suppress cirrhosis and cancer, antimetabolite is taken for a long time. (25% of patients with hepatitis B positive may develop either cancer or cirrhosis).

**Cancer**

very very bad like AIDS. cancer is present here in Jordan but not that much because we don't drink alcohol, or use oral contraceptives, but we smoke, stress can cause cancer , but the problem is growing adapting western life style is increasing cancer levels.

cancer is not one disease but 200 different diseases.

Good luck , Merry Christmas and Happy New year