PHARMACOLOGY

◉ Sheets ○ Slides

Number: 6

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Subject: Pharmacokinetics

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****This sheet was written according to the record that belongs to section 3.**

****Before we start the topics of this lecture,**

In the previous lecture, Dr. Malik mentioned –by mistake- wrong information in one of the sections saying that estrogen causes osteoporosis.

At the beginning of this lecture, the doctor emphasized on the fact that **Estrogen does not cause osteoporosis**. In fact, estrogen is used to treat osteoporosis, and can cause strokes (a woman who is taking estrogen for the purpose of treatment of osteoporosis may develop a stroke).

❖ Topics of this lecture:

* Risk factors for adverse drug reactions
* (Risk: Benefit) ratio
* Social sciences and Pharmacology
* Variation in drug responses
* Pharmacogenetics and Personalized medicine

❖ Risk factors for adverse drug reactions

Factors that make a patient more susceptible to adverse effects (most of them were discussed in previous lectures):

1) Simultaneous use of several different drugs "polypharmacy".
   -due to increased chance of drug-drug interactions.
2) If the patient is very young (pediatric patients) or very old in age (Geriatric patients).
3) Pregnancy.
4) Breast feeding.
5) Hereditary factors.
6) Disease status.

❖ (Risk : Benefit) ratio

- (Risk : Benefit) ratio is in fact what pharmacology is all about.
- Pharmacology is all about the balance between risk and benefit (between the adverse effects and the therapeutic effects).
- With every drug use, unwanted effects must be taken into account. Before prescribing a drug, the physician (doctor) should ,therefore, asses the (risk : beneft) ratio.
- According to what we have learned in pharmacodynamics, it's important to note that this ratio is dynamic (not static), due to differential pathophysiology, differential age, gender, and other factors.
  In other words, the (risk : benefit) ratio in children is different from that in adults, and the ratio in elderly is different from that in children, and so on.
- *Some points mentioned in section.1:*
  There are no drugs without side effects(that's because receptors exhibit homology which means that no single drug can bind to a single type of a receptor 100%, a lesser amount(4-5%) of the drug binds homologous receptors) but we take the risk and prescribe the drug when we believe that it will benefit the patient more than it will harm him through its side effects.
  Examples:
  1)*anti-cancer drugs (the risk is high, but the drug is the only way to save the patient's life)*
  2)*doctors usually don't prescribe anti-viral drugs in cases of normal flu, because there is a high chance (risk) that the influenza virus will get resistant to tamiflu which is the only drug that can treat flu.*

❖ Social sciences and Pharmacology

- As a doctor, you really need to communicate with your patient.

- Whenever you are telling your patient information about a certain drug, it's important to:

  1) Speak clearly and slowly
  This is very important because it is necessary to make sure that the patient understands what you are saying, otherwise, your patient may get scared.

- You should use simple words and take into consideration the level of your patient when you speak to him.

2) Be aware of different languages and cultures.

3) Know that patients will sometimes have a different meaning than the person teaching the information.

➔ This is clinical pharmacology, you really need to teach your patient.

- The following hints must never leave your mind as a physician when you are dealing with a drug:

1) Balance between over-prescription and under-prescription.
Don't be over-strict and never prescribing a certain drug that may have a toxic material and may cause an adverse effect to your paient (under-prescription). At the same time, don't prescribe multiple drugs whenever you see a paitent (over-prescription).

- It's important to balance between over-prescription and under-prescription.

2) Avoid a pill for every ill.
Try not to treat each and every disease with drugs, always consider non-pharmacological therapy.
Examples:

1- If a patient has developed hypercholesterolemia/hyperlipidemia (high lipid concentration in his blood), the treatment may be through changing his life style (by decreasing fat intake in his diet). In this case try to avoid prescribing a drug to this patient because if an anti-hyperlipidemic drug is prescribed to him, he will take it for the rest of his life

2- If a patient has diabetes mellitus, try to avoid prescribing drugs. Many patients with diabetes mellitus can stay 20-30 years without taking drugs (through commitment to certain diet, and this is realted to the nutrition field).

Three steps in planning to give a medication:

1) Decide the reason or goal for giving the medication.

2) Learn specific information about the medication:

a. The desired action of the drug and how the drug acts.

b. What are the possible adverse side effects and drug-drug interactions that may develop.

c. The usual dosage, route, and frequency.

d. Contraindications (محاذير الاستخدام) : the situations in which the drug should not be given. For example, drug (A) is contraindicated in pregnancy, this means that drug (A) must never be given to a pregnant woman.

e. Drug interactions (what is the influence of another drug given at the same time?).

Note: the previous 5 points must be known before prescribing any drug. In the next lectures with Dr. Hamzeh, these five pieces of information about drugs that we will study are going to be very important.

Note.2: in cases of contraindications, if a doctor gives a drug to patients who should not take it, the doctor can be sued legally.

3) Develop a teaching plan for your patient.

Don't let your patient get scared of the drug. As an example:

If when using drug X (for example, metformin, that is a very safe drug used for treatment of diabetes mellitus type 2), one out of 10,000 patients may develop kidney failure (this is considered a very rare side effect). In this case, don't let your patient get scared of using this drug.

That's why precision is needed. Internet websites may sometimes mention information as the following: "this drug may cause kidney failure", and this is a wrong way of introducing information. You have to be scientific, you should care about the frequency of the adverse effect(in how many patients does the adverse effect occur?) like kidney failure due to the use of Metformin.

Don’t tell the patient: "this drug is good but it causes kidney failure", because he might get scared and decide not to take it.

Note: Glucophage is the trade name for metformin (metformin is the generic name). Glucophage is sometimes used to cause weight loss, but actually it doesn't.

You have to have a teaching plan for telling the patient:
a. what he needs to know about the medication's action and side effects. (not every thing should be said to the patient, *don't tell him very rare side effects*).

b. what he needs to know about the administration of the medication. You should also tell him that if he doesn't take the drug at the prescribed times, the drug will be under the therapeutic level.

c. What he needs to report to the nurse or physician about the medication, for example, telling the patient:" if X happens, call me".
This is actually very common in treatment. Sometimes drugs cause side effects but we can't know for sure which patients are going to develop these side effects (this is due to many reasons discussed in the last lecture like having different sensitivities to the drug, allergy,...)

As a summary, you need to sit with your patient and tell him about the drug, and of course you should as a doctor know enough information about the drug you are prescribing.

❖ Variation in drug responses

Sources of individual vriation: (why do people respond to drugs differently? Why do people develop side effects differently?):

- Age
- Sex (gender)- due to hormonal differenes.
  For example: a drug called Zolpidem (a hypnotic منوم)-treats insomnia(الأرق). Previously, doctors used to prescribe this drug ,for both men and women, in doses of 10mg. but few years later, it was found out that many women suffer from hangover (a side effect, it means waking up in the next day feeling dizzy) while men don't. Now, it is recommended to give women 5mg of zolpidem while giving men 10 mg of this drug. Zolpidem is the first drug to be given in different doses according to gender.

In both cases (giving this drug to men or women), the therapeutic activity (the hypnotic activity) is the same. Nevertheless, the 5mg-dose prescribed for women causes less adverse effects.

- Weight, less effective and longer lasting in obese individuals(storage in fat,affecting the volume of distribution).
- Kidney and liver function- this is related to the rate of elimination of the drug.
- Genetic variables- tolerance, allergy (though not always genetic).

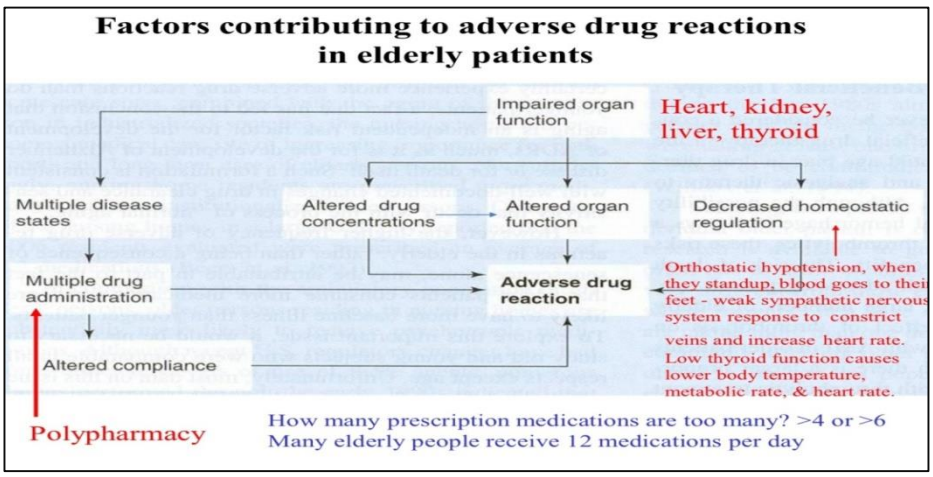
The main source of variation that we can deal with -and improve the situation in- is Genetic Variables. The other sources may cause variation in drug responses **normally** without a clear reason, but genetic changes that can cause variation in drug responses are usually more clear reasons for vriation.

Related to variations are the changes in <u>pharmacodynamics</u> in geriatric patients, age realted changes include:
(note: you're not required to memorize the names nor the actions of the drugs in the following examples)

- Increase in the sensitivity to sedation and psychomotor impairment with benzodiazepines. (consider them drugs X and Y for example).
- Increase in the level and duration of pain relief with narcotic agents.
- Increase in drowsiness and lateral sway with alcohol.
- Decrease in the heart rate (HR) response to beta blockers.
- Increase in the sensitivity to anti-cholinergic agents.
- Increase in the cardiac sensitivity to digoxin.

There are age related changes in both, pharmacokinetics and pharmacodynamics.

Geriatric patients should be well-monitored beacause they have different kinetcs and different dynamics, that's why these patients are grouped in a special group; "geriatric group".



Notes concerning the previous figure:

- Geriatric patients are usually polypharmacy patients.
- They may have impaired organ function which leads to:
  1) altered organ function 2) altered drug concentrations
  3) multiple disease states 4) decreased hemeostatic regulation
  All of these consequenses make the patient more susceptible to adverse effects.

Pediatric patients are also a special group.

- Children are not small adults.
- Distribution, metabolism, and elemination processes are different in children compared to other groups.

Pregnant ladies are also a special group *(the following points were mentioned in section.1)*

- *In pregnancy, the drug is really going to two people, so you must consider how the drug may affect the growing fetus.*
- *It's important for women to avoid as many drugs as possible unless ordered by the physician. (don't ever prescribe a drug to a pregnant woman unless she really really needs it, because there is a high risk that the drug used may cause problems in the fetus (malformations)).*
- *You may wonder why drugs aren't tested to see if they affect the fetus or not. In fact, **ethically**, we can't test drugs on pregnant women. That's why there are many drugs that haven't been tested in relation to teratogenesis(producing congenital malformations in the fetus).*
- *The doctors may sometimes hesitate when they prescribe a certain drug due to the absence of studies that reveal if it affects the fetus or not.*
- *Classification of drugs related to pregnant ladies:*
  Drug X → *the drug should never be given to pregnant ladies because it has been reported to produce malformations in the fetus.*
  Drug D →*it has been reported to cause malformations in animals but haven't been tested in humans.*
  Drug C → *haven't been tested*
  Drug A → *not important for you to know*
  (just focus on types X and D)
- *Type X drugs are known through history. For example, pregnant women previously used to take thalidomide to treat nausea and vomiting, this caused their babies to be born with short hands (داء الفقمة).*

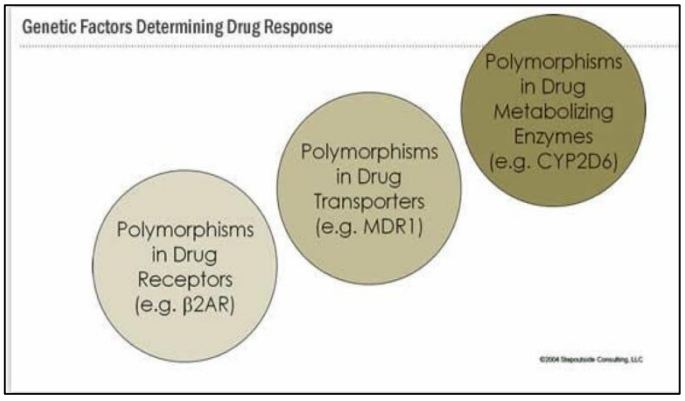
- *Most of drugs will not harm pregnant ladies but we always try to avoid even the 1% risk in pregnancy.*

❖ Pharmacogenetics and personalized medicine

Currently, we are in the era of dreams about personalized medicine; that is to prescribe drugs according to the genetic component of our patient.

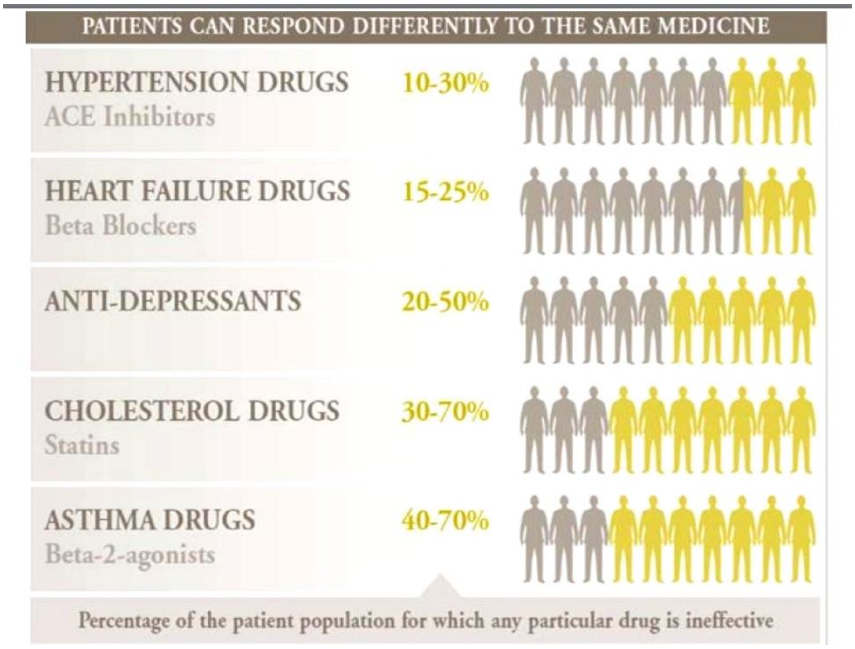
The genetic component of the patient affects mainly three groups of proteins that control the movement and the activity of the drug in the body. These three protein groups are: (the figure below)
1) Drug receptors
2) Drug transporters (example: MDR1 (P-gp1))
3) Drug metabolizing enzymes

If one of these three is different, the way we deal with the drug is going to be different.



If we **normalize** our patients, we may increase the response rate, in other words, we may decrease the non-despondence rate.

If we give a drug to 100 patients, not all of them will really benefit from the drug. The following figure shows the percentage of the non-responders to a group of drugs. For example, 40-70% of patients who take anti-asthmatic drugs don't really gain benefit from these drugs (non-responders).



In real life, if we give a certain drug to 100 patients, in most cases, 50-70% of patients will respond and approximately 30% will not.

One of the ways to increase the number of responders and decrease the number of non-responders is **normalization** (to normalize drug level).

How to normalize drug levels?

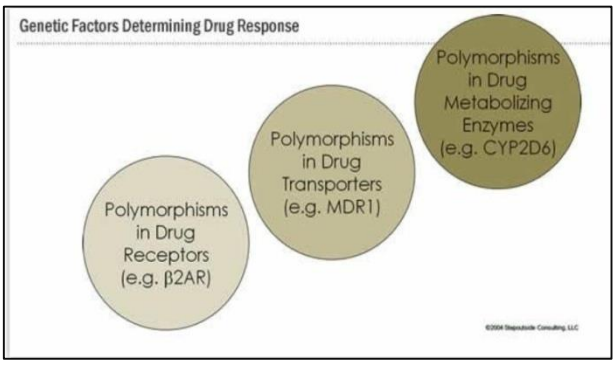
To answer this question, we should first know the meaning of Pharmacogenetics and personalized medicine.

- Pharmacogenetics is the study of the effects of a drug in relation to a single or defined set of genes.
- Personalized medicine means the prescription of specific treatments and therapeutics best suited for an individual's genetic makeup.
- Personalized medicine will enable doctors to:
  1) Use medications and other treatments that would work best for each individual.
  2) Avoid medications that would cause an individual to have bad side effects.

In non-responders:

The non-respondence (absence of response) may be due to one of the following:

1) The drug receptor in these patients isn't working or not having a good affinity towards the drug.
2) Transporters are different in these patients.
3) the drug metabolizing enzymes are different or subjected to mutations
   → This may cause different effects and side effect (different from those in the normal cases)

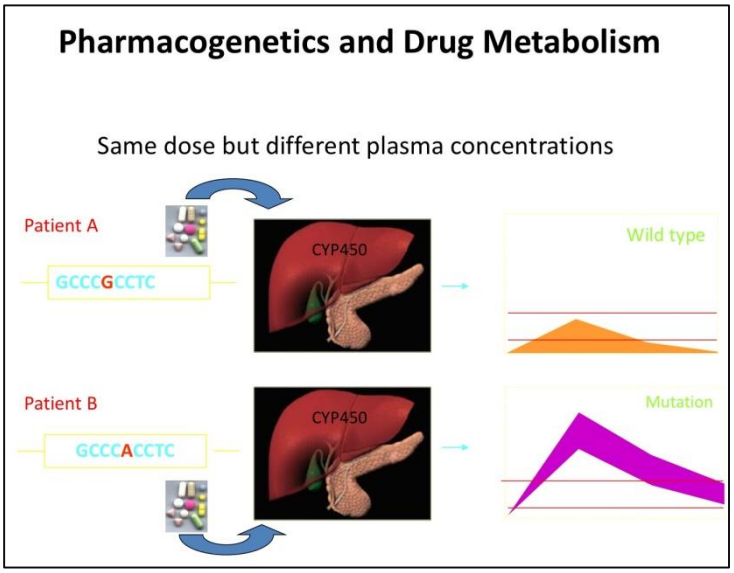


<u>Example</u> (on polymorphisms in drug metabolizing enzymes):

If a patient has a mutation in the metabolizing enzyme, he will deal with the drug differently.

In this example, (the figure on the right):

- The normal situation is to have (G) nucleotide in a certain place in the DNA sequence.
- If the patient has (A) instead of (G), this is called single nucleotide polymorphism (mutation).



→ This results in nonfunctioning metabolism in the enzyme coded by this sequence.

→ This causes the concentration of the drug (that is metabolized by this enzyme in normal conditions) to get raised massively (the curve at the bottom right in the figure) causing more side effects.

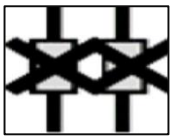
(This example is on the level of drug metabolism.)

<u>Note:</u> Polymorphisms may occur in CYP2D6, CYP3A4, or any other CYP.

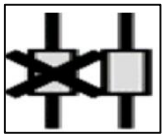
In order to normalize (or personalize) medicine, we need to classify patients into 4 groups according to the functioning of CYPs.
Let's consider CYP2D6, the 4 groups are:

1) Poor metabolizer (PM)
Remember: every gene has two alleles

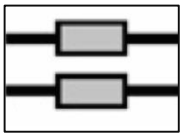
- Has low metabolic activity
- Has two mutant alleles. (Patients with PM CYP2D6 have mutation in both alleles responsible for the enzyme).



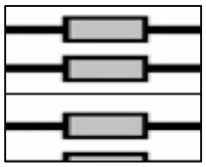
2) Intermediate metabolizer (IM)
The patient is heterozygous (one allele is mutant, the other is normal).



3) Extensive metabolizer (EM) or normal metabolizer
No mutations at all, full functioning alleles.



4) Ultra-rapid (or Ultra-fast) metabolizer (UM)
The gene-due to increased need for the enzyme in our ancestors- has undergone multiplication which resulted in multiple alleles (not only two alleles, instead, it may have 5, 7, or 10 alleles for example).



- According to every single enzyme, we classify our patient
- The same person may be PM at CYP-2D6, IM at CYP-3A4, and so on.
- When do we care if our patient is poor metabolizer in CYP-2D6?
  If the drug that is prescribed for this patient is metabolized by CYP-2D6.

How can we know this classification? (How to know the phenotype of the CYP in the patient?)

- When a baby is born, we can know the genetic component of his whole genome (sequencing the genome).
  **These are dreams but will be reality in few years, and currently, such techniques are used with cancer patients. **
- After knowing the genetic makeup of this baby, a file can be saved on the computer, this file contains the sequence of this patient's genome. If he has single nucleotide polymorphisms, they'll be mentioned in this file. In addition, his classification as poor metabolizer or intermediate or

excessive...at the level of certain enzyme will also be mentioned, and when we want to prescribe a drug, all we should do is to enter the drug's name and the computer will warn us if the patient is –for example- poor or intermediate metabolizer for this drug.

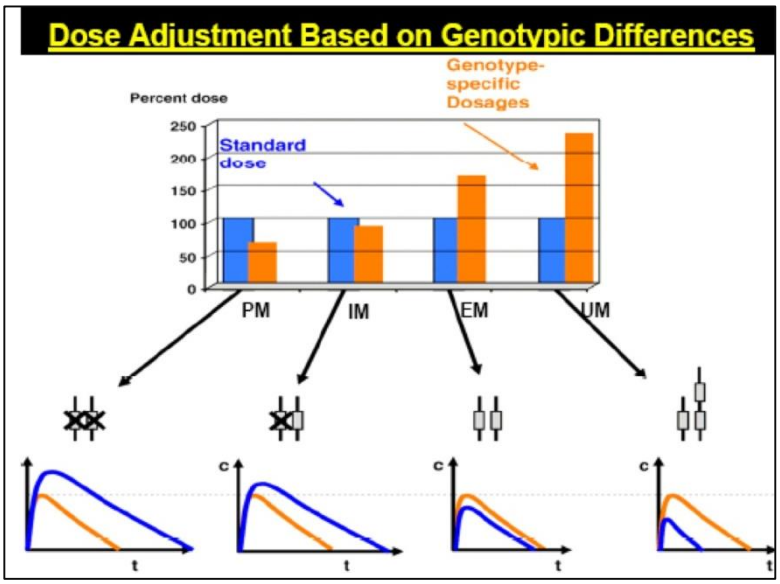
Knowing all the previous information about classification of patients, how can this be beneficial to doctors??

the dose given to the patient will be according to his phenotype (the patient's metabolic activity of that enzyme).

- Patients who has poor metabolizer enzyme **(PM)** → we will prescribe a little amount of drug.
  (because the drug won't be metabolized, so it will stay for a longer time. That's why we prescribe a little dose. Higher doses will elevate the concentration of the drug (the curve gets higher) and may reach the toxicity level.
- **(IM)** → higher dose than that in the case of (PM).
- **(EM)** → higher dose than that in the case of (IM).
- **(UM)** → higher dose than that in the case of (EM)

Why do we consider the previous differnces in doses?
To normalize (personalize) the drug level (note that the curve with the lighter color in the figure below is the same in all 4 cases).

How did this normalization occur?
By changing the dose according to the classification.
If all 4 groups were given the same dose, they will produce different kinetic profile (look at the curves with the darker color). We compensate this difference in kinetic profiles by giving different doses.



→As a conclusion, every patient may require a different dose and this is "personalized medicine", we don't prescribe the same dose to all patients, we prescribe different doses according to their genetic component.
(The doctor predicted that these processes will bocome a part of our lives in 2020).

The situation is not the same in the case of prodrugs.

- What is a prodrug ?? (الدواء غير المفعّل)
  A drug that is activated when it goes through the first-pass metabolism.
  Example: some drugs are taken orally as tablets, they reach the stomach, then they get absorbed, after that, thay reach the liver to get metabolized. This metabolism causes the activation of the drug instead if deactivation-as in the case of normal drugs-.
- When we are dealing with a prodrug:
  Patients with **(PM) enzyme** → require high doses (because the metabolism is poor, activation is poor, so we need a high dose)
  (IM) → lower dose than that in the case of (PM).
  (EM) → lower dose than that in the case of (IM).
  (UM) → lower dose than that in the case of (EM).because the drug is activated quickly so we need to decrease the dose.

The following few points are only to understand where polymorphism –in CYP2D6 for example- came from, and not to be memorized.

- CYP2D6 is an important enzyme that is responsible for metabolizing 25% of drugs we use.
- If a person lacks CYP2D6, this means that 25% of drugs he take may develop side effects in his body due to elevated drug concentration (as a result of the deficiency of metabolism processes).

- Many many years ago, people in certain places like Ethiopia used to eat plenty of spicy food. In these populations, the UM form of CYP2D6 developed. That's why we find that in Ethiopia, the percentage of people with UM form is 29%. (highest percent→Ethiopia is the origin of UM)
- Part of this population migrated then to Yemen, that's why the

percentage in Yemen is 20 %.

- Part of Yemen's population migrated to Jordan, the percentage in jordan is 13%.
- Spain, 10%.
- Middle Europe, 3-6%.
- North Europe, 0-1%.
- The previous points are only to justify the stement that says," different populations have different frequencies for genetic mutations". Genetic mutations come from the environment.
- An example realeted to the previous statement: sickle cell anemia in sub saharan africa is very common because malaria was very prevalant. Many years ago, and in order to resist malaria, single nucleotide polymorphism (mutation) occurred in globulin gene resulting in higher chance of sickle cell anemia occurance in those populations.
  (percentage of people that have mutation in globulin gene in sub saharan africa is much higher than that in jordan, as a result, percentage of people with sickle cell anemia in sub saharan africa is higher than that in jordan).

Pharmacogenetics or personalized medicine may be targeted towards the drug receptor.

Examples:

1)) Salbutamol (Albuterol) receptors-treats asthma-

- Within the normal population, position 16 in the amino acids sequence of the **β2** receptor contains arginine. Remember that two alleles are responsible, which means that in a normal **β2** receptor, we have Arg/Arg. (2 Arginines, one for each allele).
- If the activity of the receptor is intermediate → Arg/Gly.
- If the receptor is not working → Gly/Gly. (Arg is absent in both alleles at position number 16).
- Response to salbutamol: *(can be known by experiment, the patient is given salbutamol for certain period of time and then we see if he responded or not, but if we are talking about personalized medicine, that means that we can know the amino acids present even before prescribing the drug)*
  Arg/Arg → patients respond.
  Arg/Gly → moderate responders.
  Gly/Gly (16% of population) → patients don't respond because salbutamol tries to bind to the receptors, it will bind, but the affinity will be very low due to the mutation that happened in the binding site.

- We treat the patient according to the previous information:
  Arg/Arg → we give salbutamol.
  Arg/Gly → we give salbutamol, higher dose.
  Gly/Gly → in most cases, the drug has to be changed, we don't give salbutamol.

  →Again, this is called personalized medicine treatment (according to the genetic component of the patient).
  Note: personalized medicine increases the number of responders. In USA, these techniques are more common than in our populations, that's why the number of responders there is higher.

2)) certain receptors related to breast cancer.

- There are different types of breast cancer. *(targets of therapy are different too)*
- We classify the patient according to the genetic component (after sequencing) and then prescribe the suitable drug.
- For example (and this is applied in Jordan),
  If the patient is ER+, meaning that her breast cancer is estrogen positive, we prescribe tamoxifen. *(Because the target of tamoxifen is present in her cancer)*
  If the patient is ER-, we don't prescribe tamoxifen.
  If the patient is HER2-positive, we prescribe Herceptin.
  If the patient is HER2-negative, we don't give Herceptin.
  - ➔ Again, this is personalized treatment. *We prescribe the drug if the patient has the target of my drug.*
    Note: drugs we care about most in this field are drugs with narrow therapeutic index like anti-cancer drugs.

-You can refer to the last page for extra information (added by the correction team) :-)

I apologize for any mistake I may have made.

Wish you all best of luck: D

Enhance your knowledge**

... (The doctor didn't mention this)

-Adrenergic receptors;

Receptor	Location
α1	Smooth muscles
α2	GI tract
β1	Heart
β2	Smooth muscles

-Regarding CYP2D6;

Cytochrome P2D6: an enzyme, which is primarily expressed in the liver. It's involved in the metabolism of xenobiotics.

Xenobiotics: A **xenobiotic** is a foreign chemical substance found within an organism that is not normally naturally produced by or expected to be present within that organism. It can also cover substances which are present in much higher concentrations than are usual. Such as drugs, chemicals and pesticides.

Type 1 diabetes vs. Type 2 diabetes -in brief-

DM1... caused by destruction of the cells of the pancreas that release insulin by the body's immune system, eventually, eliminating insulin production from the body, accounts for 5-10% of people who have diabetes. Managed by insulin injections.

DM2...the body isn't able to use the insulin efficiently due to a problem in the insulin receptors or signal transduction pathway, accounts for 90% of people who have diabetes. Managed by a low-carbohydrate diet and weight loss.

Read only