Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 13

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بسم الله الرحمن الرحيم

If you remember, in the previous lecture we talked about geriatrics, which are special population with special body composition and we mentioned for example that they are more sensitive for analgesics(they need less analgesics) and that's because they have different level of activation of the sympathetic nervous system.

Pediatrics:-

You need to keep an eye on pediatric patients because they're really different.

- Pediatrics , Geriatrics , Pregnant and lactating ladies we call them special population .. why ?

1) We don't test drugs on them.
2) They have different body composition.

There are variations in drugs response in the special populations that are not taken in consideration sometimes because we don't test the drugs on them we test them on Adults

Our base line is normal adults between 20 & 60 years. Those are the category that we test drugs on (clinical trial).

- It's not your responsibility as a second year medical student to know everything about those special populations. But you have to understand that they're different, because they have different body physiology.

How is pediatrics body composition different than adults?

1- They have higher proportion of water. About 75% of their body mass is water, compared with 65% in adults.
2- They have less fat.
3- They have lower plasma proteins level which will increase drug bioavailability because there are less plasma proteins available for the drug to bind to so the amount of free drug concentration will elevate in the blood .
4- Immature liver & kidney.

- Liver often metabolize more slowly.
- Kidney may excrete more slowly.

◎ Simply speaking, the child is not yet mature to deal with drugs. As a result, some drugs are contraindicated in children, but given normally to adults. So, we have to be aware while prescribing any drug to a child.

*examples:

- You're not allowed to give brufen to a child under 6 months. Simple? Very simple ☺

- You shouldn't prescribe diclofenac for a child less than one year.

- Rocephin (antibiotic) shouldn't be taken by a child before 28 days.

➘ Why there are such contraindications in these drugs administration ?

It's all about children maturation & development. Take Rocephine (generic name: ceftraxione) for example, infants usually have Hyperbilirubinemia **>>>**high billirubin. Bilirubin has an interaction with this drug; it binds to it & precipitates in lungs and kidneys (this only happens with infants with an age of 28 days & less).

◎ The bottom line of the story: children are very sensitive toward drugs. It's very difficult to deal with children. Although, infants are different than children & children under 12 years are different than those above 12 years and so far so on. >>> You need to know if a drug can be prescribed to a child or not. And even if it's prescribed to a child, it needs what we call drugs monitoring.

◎ For example EXTRAPOLATION is a method used in dosing drugs to adults based on their weight and surface area .

➘ It's a huge mistake to do Extrapolation on children because their body physiology is different .children are not small adults. For example, an adult patient (100 Kg) & a child patient (20 Kg) , so I give the child fifth of the adult's dose based on extrapolation this is totally wrong since the relationship is not linear.

◎ Pediatrics problems:

- Absorption may be less or more than adults. (kinetics)

- Clearance of some drugs in children is affected by maturation, cytochrome P450 system matures over time, glomerular filtration changes over time. (kinetics)

*examples:
- Clearance of midazolam by CYP3A4 & CYP3A5 goes from 1.2 ml/min/Kg to 9 ml/min/Kg over first few months of life>>> what you prescribe to one month old infant differs from what you prescribe to 6 months old infant for example.

- Carpamezapine (3A4) clearance faster in children than adults>>> require higher doses.

دكتور خربطتنا ☹ Do we have to give children higher doses or lower doses? Usually we give lower doses but there are some exceptions (like carpamezapine which is an antiepileptic drug) , when you prescribe carpamaezapine for children you need to give higher dose than adult because the clearance of that drug in children by CYP3A4 is faster than adults

- Drug targets may vary with age. (dynamics)

↘ Remember: receptors are dynamic; they change according to the environment & development.

◎ What to do with children? Always try to start with the smallest dose then titrate up (increase the dose while monitoring your patient)… titration is the opposite of tapering (dose decreasing). I think it's simple ☺

If you're not a pediatrician, don't prescribe a drug to a child unless it is a wide therapeutic index drug.

◎ Dealing with pediatrics is more difficult than dealing with geriatrics.

Pregnancy

◎ Never ever prescribe a drug for a pregnant lady, except if she's in a real need for it. Because as we said before, drugs aren't tested on pregnant ladies.

◎ In pregnancy, there is a risk of teratogenic activity (malformations/effect on fetus). The physician must know if the drug is teratogenic or not. Of course teratogenic drugs –that are likely to cause malformations or damage for the embryo or fetus- are avoided!

We can't test a drug on a pregnant lady, instead we can test it on a pregnant mouse >>> if it has a malformation effect on mice, we avoid giving it to a pregnant lady. But the problem is: if the drug doesn't cause malformations in animals, does it exclude malformations in humans? <u>NO! That's why drugs are avoided as much as we can during pregnancy.</u>

*example: in the 60s & 70s, pregnant ladies used to take an antinauseatic drug called thalidomide. One of the side effects of Pregnancy is high nausea & vomiting and sometimes because of that a pregnant lady can't eat for a few months ,This drug was tested on animals & didn't cause fetus malformations, but it caused malformations in humans >>> babies were born with something called: داء الفقمة. (very famous) it's characterized shortness and atrophy in limbs

◎ Drugs are classified into categories according to their effect on human fetus :

1. category X :-drugs approved to have teratogenic activity on human fetus
2. category D drugs caused malformations in animals & there's no knowledge if it causes humans malformations or not)
3. category C drugs that didn't cause malformations in animals, but no study was done on humans , They are the most commonly used drugs .
4. categories A & B are safe.

↘ Drugs of categories D & X must be avoided , These Categories are written on the leaflet of each drug .

*example: pregnant ladies may undergo hypertensive pregnancy it's Treatment is different than the treatment of any different hypertension. We use a drug called methyldopa which is a very old drug that is not used on normal hypertensive patients but used in hypertensive pregnancy Why? Because it's free of teratogenicity.

- Can a drug go from category C to category A or B?
  It's possible but it doesn't exist. (till now)

Pregnant ladies physiology:

- Decreased GI motility. It's very common to have constipations or hyperacidity & signs of reflux during pregnancy.
- Nausea & vomiting
- decreased absorption and lower plasma drug concentration.

◎ Conclusion: don't give a drug to a pregnant lady unless she's very very sick & avoid tetratogenic drugs.

Pharmacogenetics

(New updating science/ the effect of genes on drugs)

Genetic variability>>>different drug response & different side effects.

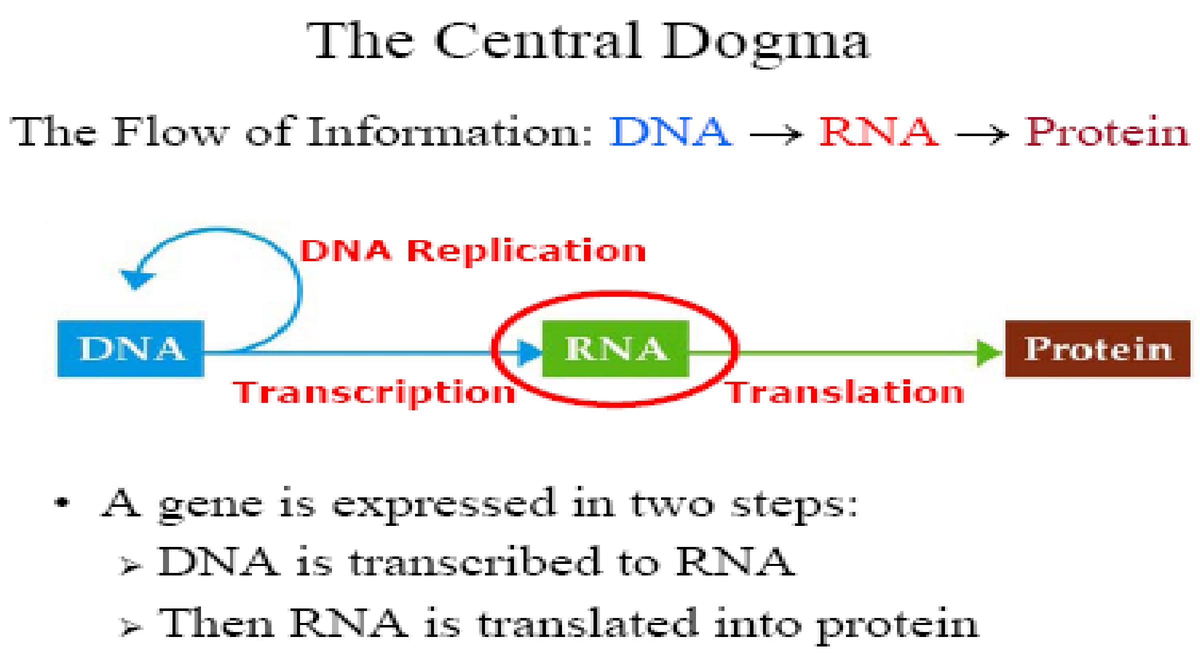
Pharmacogenetis: the study of the effect of a drug in relation to a single or defined set of genes.

The goal: rational means to optimize drug therapy & ensure maximum efficacy with minimal side effects ☺

We need to know the genetic component of a patient, because this is what causes the patient to deal differently with the drug.

Proteins come from genes (we have about 30,000 genes). In pharmacology, we're interested in proteins which are: the receptors, metabolizing enzymes & drug transporters in our bodies.

Different genes>>> different protein (change in dynamics & kinetics) >>> different response. This is not always true; the drug may have the same transporters, targets & metabolizing enzymes in the two individuals causing the same response & side effects. (no polymorphism)



Amount of variability depends on the protein involved in the process (is it different between the individuals or not).

*examples:

- We differ in the effectiveness of p-glycoprotein transporters or NDR activity.

- Ventolin binds β-2 receptors & produces bronchodilation. Simple?

In 10-20% of patients it has no effect. Polymorphism changes the structure of receptors>>> no binding>>> no therapeutic effect & different response.

SNPs (single nucleotide polymorphism): a site of the DNA in which a single base-pair varies from person to person. They're the most common form of genetic variation in human genome (frequency >1%).

It's some sort of mutation. But when its frequency <1% we call it mutation. Mutations indicate a disease but polymorphism doesn't change the phenotype & only appears in drug response.

We have 3 billion nucleotides in each cell. Nucleotides sequence is 99.9% identical & we only vary in 0.1% (about a million) of nucleotides. These differences are between each two of us except for identical twins. And of course, differences between Jordanians & Chinese are more distinct. >>> Different ethnicity.

*examples on ethnicity:

- We're different physiologically because of different genetic material between us & Africans. Africans have more muscles' mass & more contracted smooth muscles>>> different drug effect.

In hypertension treatment: Africans respond very well to diuretics (they have nothing to do with muscles). On the other hand, they do not respond to β-blockers or to ACEI (cause contraction of smooth muscle).

Different nucleotides sequences lead to <u>DIVERSITY</u>. Diversity leads to different genes.

We're close to our generation but there's a distinct difference between us & the previous generations, for example.

- We want to emphasize the idea of "personalized medicine" a new era of medicine. It's not enough to prescribe the drug for all the population; we want the pill to be prescribed specifically for each patient.
- For some drugs we have to test whether our patient is positive or negative (does he have the protein or not).

*example: we have a drug called herciptin used for breast cancer. Breast cancer differs between individuals with different genetic components. Some patients have over-expression of a receptor called HER-2 (20-30% of breast cancer population). So, we only prescribe the drug for those 20-30%.>>> personalized medicine.

Personalized medicine: the prescription of specific treatment & therapeutic best suited for an individual's genetic make-up. P: بتخيل إنها سهلة

This exists in the U.S not in Jordan, except for king Hussein cancer center.

- Use medications & other treatments that would work best for the patient, and avoid what causes bad side effects.

Best wishes doctors!
Razan Jaras ☺