TOXICITY CAUSED BY GENETIC INDIVIDUAL DIFFERENCES IN DRUG USE

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GENETIC VARIATION

Variation (Diversification) are differences that can occur within or between populations, observed within species or gene alleles.

This genetic event causes individuals or groups within a species to have distinct features. (E.g.): People of different sizes, nose length, shortness, straight or slanted eyes, color difference of roses, shape differences in fruits, etc.

Variations:

1) Hereditary variations (Genetic variations)
2) Non-hereditary variations (Modifications)

Factors affecting genetic variations:

1) Polymorphisms
2) Mutations

Modifications

They are non-hereditary changes observed in the living organism's external appearance under the influence of non-hereditary factors.

The scar color that occurs as a result of any accident or when we dye our hair cannot be transferred to the offspring by heredity.

GENETIC MECHANISM

The inheritance units, genes, are located on chromosomes and are part of the DNA molecules. Each of the gene pairs located in the same places of the chromosomes is called "allele".

In humans:

23 pairs of chromosomes

22 of them is autosomal,

1 of them is sex chromosome

Sex chromosomes;

In women XX

In men XY

Inheritance with a gene located on the X or Y chromosome is called "sex-linked inheritance".

As a result of the change in genetic structure, especially enzymes and receptors are seriously affected. Due to these changes, several diseases have been seen in individuals.

Especially

1- Genetic changes cause changes in the pharmacokinetics of drugs in individuals and affect the toxicity of these drugs, since the biotransformation of drugs depends on metabolic changes caused by enzymes (pharmacokinetic changes).

2- In addition, due to genetic disorder, receptor proteins may occur in qualitative and quantitative differences. Thus, individuals respond differently to the chemical or drug (pharmacodynamic changes).

IDIOSYNCRASY

Abnormal response to drugs and chemicals due to hereditary reasons.

CHANGES IN THE PHARMACOCINETICS OF THE DRUG RESULT OF GENETIC CHANGES

Deficiency or inactivity in the gene coding the enzyme as a result of enzyme polymorphism causes the drug metabolism to change through this enzyme.

The phenotype in which the synthesis or structure of the enzymes responsible for drug metabolism is impaired is called the slow metabolizer,

and the normal phenotype is called the rapid metabolizer.

Alterations in drug metabolism causes changes in toxicity or detoxification.

Example: The slow inactivation of isoniazid and similar drugs

Isoniazid is an antibiotic drug that is used in tuberculosis treatment.

Isoniazid, Hydralazine, Sulfonamides, are inactivated in liver by N-acetyltransferase.

In the ones who acetylise slowly, peripheral neuropathy is seen while some hepatotoxic effects seen in the ones who acetylise fast.

Example: Alcohol related reactions

In recent studies it is proved that the speed of the alcohol metabolism shows variability due to the genetic differences.

When Japanese and Red-indians people drink alcohol their faces turn to red.

This fact is because of the existence of an "atypical" alcohol dehydrogenase enzyme which transforms alcohol to acetaldehyde rapidly.

When these people drink alcohol, their skin turn to red due to the excessive acetaldehyde levels in their blood.

Then due to the change in the $NADP^+$/NADPH ratio, the transform rate of the alcohol to acetaldehyde decreases so the redness stops.

IN USA, the studies show that, the 90% of the caucasians have the enzyme that metabolize alcohol slowly bu ton the contrary, the 90% of the yellow race have the enzyme that metabolize alcohol rapidly so that the people from yellow race have the risk of redness in their skin after using alcohol.

Example: Another reaction related with alcohol is that people using chlorpropamide and tolbutamide as oral antidiabetics, when they drink alcohol with these drugs their skin turn to red also.

In these individuals, the slow form of aldehyde dehydrogenase is obtained. Chlorpropamide and tolbutamide inhibit this enzyme and this fact occurs.

Example: Hydrolysis of Succinylcholine.

Succinylcholine is a drug used for short-term paralysis in striped muscles. It is inactivated by hydrolysis of plasma pseudocholinesterase enzyme to succinyl monocholine. The inactivation is very short so that its paralysis effect continues for only 5 minutes by intravenous route.

In England, 95% of the population is homozygous. In regards of atypical gene, the enzyme activity in homozygous ones is decreased to 50% so that in these people the effect of succinylcholine is prolonged resulting in long lasting muscle paralysis.

CHANGES IN THE PHARMACODYNAMICS OF THE DRUG AS A RESULT OF GENETIC CHANGE

Example: Hereditary Methemoglobinemia

Cyanosis develops when the people whose white blood cells don't have methemoglobin reductase, use the drugs such as

- nitrite,
- phenacetin,
- The other aniline derivated analgesics,
- nitrobenzene derivates

which transform hemoglobin to methemoglobine. This genetic disorder is called, Hereditary Methemoglobinemia.

In normal persons, 1% of the hemoglobin in red blood cells (RBC) is methemoglobin (includes Fe^{+3}). Ferric iron is reduced to Fe^{+2} by 4 different enzyme systems in RBCs so there is no methemoglobin accumulation.

These inducing systems:

1- Ascorbic acid
2- Glutation
3- NADPH (Nicotinamid adenine dinucleotide phosphate)
4- NADPH dependent methemoglobin reductase

Some of the drugs causing methemoglobinemia affect as DIRECT OXIDIZING EFFECT.

- Nitrites
- Nitrates
- Chlorate
- Excessive dose of methylene blue etc.

Some of the drugs and chemicals transform to oxidizing metabolites namely, INDIRECT OXIDIZING EFFECT.

- Aniline
- Nitrobenzene
- Nitrotoluene
- Aryl-amino, aryl-nitro compounds

- Acetanilide
- Sulfonamids

Drug sensitive hemoglobins

People with abnormal hemoglobin (such as Hemoglobin H, M, S) in their RBCs, are sensitive to drugs causing methemoglobinemia by oxidation (especially hemoglobin H). During exposure to oxidizing chemical or drug, methemoglobinemia develops. Haemolytic anemia can also occur.

Example: Primacine sensitivity.

People with glucose 6-phosphate dehydrogenase (G6PD) enzym deficiency in their RBCs, the oxidizing drugs itself or their metabolites cause haemolytic anemia. This syndrome is found firstly in primacine users so that this genetic defect is called as Primacine Sensitivity.

Primacine, is an 8-aminoquinoline derivated drug used in malaria. In normal persons, in therapeutic dose no adverse effect can be seen. But, in G6PD enzyme deficency, haemolytic anemia can develop even in therapeutic dose.

In primacine sensitive RBCs, reduced glutation (GSH) levels are low because of the G6PD enzyme deficiency.

Chemicals or their metabolites causing hemolysis oxidize this reduced glutathione and inactivate it.

G6PD deficiency is primarily seen in Africa and Mediterranean region people.

In Çukurova region its frequency is 11,4%, in Cyprus it is 3,5% and in Aegean region it is 1%. The highest incidence is 13 % in Saudi Arabia, and in USA Afro-Americans as 10-13%.

It was found firstly in primacine users so that this genetic defect is called as Primacine Sensitivity. Also in people who has this genetic defect consuming Fava (broad bean, Vicia faba) haemolytic anemia develops. This disorder is called as Favism.

Example: Hepatic porphyria.

Hepatic porphyria is a hereditary disease. In this disease, delta-aminolevulinic acid synthetase enzyme (δ-ALA) which is a speed limiting stage for porphyrin and heme production chain can be induced by some drugs and its level in hepatic cells gets higher.

These drugs are:

Barbiturates
Ethyl alcohol
Sulfonamides
Chloroquine
Griseofulvin

Contraceptive steroids
Benzodiazepines
Isoniazid etc.

When these drugs are taken, enzyme will be excessively induced so that porphyrin and its precursors will be more produced; the disease symptoms become clear and gets severe. At last, in acute cases porphyrin and its precursors' levels get higher in both plasma and urine. Aminolevulinic acid and porphobilinogen levels also increase.

Succynil KoA + glycine

δ-ALA

Porphobilinogen

Uroporphyrinogens

Porphyrins

+ Fe^{+2}

HEM + protein HEMOGLOBIN

GAINING RESISTANCE AGAINST CHEMICAL SUBSTANCES

In some kinds and in the different individuals belonging to the same kind gain resistance against several chemicals and drugs by induction of metabolic processes genetically. This fact protects these kinds against the toxic effects of these chemicals and drugs.

Example: In rabbits atropinesterase enzyme level is very high. This protects these animals against the effects of atropine.

Example: Some bacteria strains are resistent against the bacteriostatic agents;
Some house flies are resistent against some insecticides such as DDT.

COMPLEX TOXIC EFFECTS DUE TO THE CONTINUOUS RESENT OF CHEMICAL SUBSTANCES'

Accumulation: Chemicals and drugs start to accumulate due to their metabolism speed. If a chemical's resent speed into the organism is higher than its elimination speed; it has tendency to accumulate in the organism and exerts its toxic effects.

Lipid soluble chemicals can easily accumulate in the organism due to their continuous resent into the body. In normal situations they are inert but when the lipid tissue starts to dissolve, they become free in the blood and it can easily exert its toxic effects.

Example: DDT can accumulate in human and animal lipid tissues and exerts chronic toxicity. Because of this reason its use is forbidden.

TOLERANCE

When some drugs are used continously, the effect of the starting dose declines steadily. The döşe should be increased to see the same effect. This is called «Tolerance». It is a resistance situation which is gained afterwards.

When a person gains tolerance to a drug which is a member of the same pharmacological group, also gains tolerance to the other members of the group. This is called Cross Tolerance.

Example: When a person gains tolerance to morphine also gains tolerance to meperidine and methadone at the same time.

Tolerance can be occurred in two ways:

1. Biochemical Tolerance:

When a drug is given in repeated doses, it induces the enzyme system which inactivates itself. So that, the elimination speed of the drug is increased; the plasma drug concentration and its activity declines steadily.

Example: In chronic drinkers, the elimination speed of alcohol increases.

The decrease in the absorption of the drug from the intestine also provides a tolerance development against this drug.

TACHYPHYLAXIS

It is the quick form of the tolerance called as Tachyphylaxis or Acute Tolerance. After a drug's one dose passed, by applying other doses in succession a tolerance to the drug can be expressed in a very short time such as in minutes.

LESSON IS OVER