GENETIC TOXICITY

ASSOC. PROF. İLKER ATEŞ

DRUG TOXICITY

DRUG

Factors
Mechanisms
Other Mechanisms

IDIOSYNCRASY

Abnormal responses due to chemicals or drugs because of hereditary reasons

Idiosyncratic Toxicity

- Idiosyncratic drug reactions are reactions which of thier mechanisms can not be cleared up.
- Individual's abnormal response to drug comes from personal genetic differences.

Idiosyncratic Toxicity

- Idiosyncratic reactions can cause fatal effects even in small doses.
- They are unpredictable complex reactions that are hard to handle.

GENETIC EFFECTS
PROBLEM

- Minimum 30,000 gene
- Approximately 3 billion base-pair in human genome
- Gene-environment interactions
- Gene-gene interactions
- The cause of environmental factors on diseases
- Chance factor

GENETIC APPROACHES

- **Heredity**
  "Is genetic playing role in this case? If yes, how important is it?"
- **Connection**
  "Can we find a small chromosome part strongly affecting on an effect?"
- **Candidate gene**
  " Can we accept the effect of this special gene on X fact? The possible variations of

this gene can be associated with X fact?"

Due to the genetic differences of the individuals, the structures of the enzymes especially responsible from metabolisms are destroyed leading to several diseases.

Specially

1- Drug elimination is directly related with the enzyme-induced metabolic changes so that genetic alterations cause severe changes on pharmacokinetics of the drugs. These changes affect the drugs' toxicities.

2- Also, due to genetic disturbance qualitative and quantitative differences on receptor proteins can be occurred. Thus, the individuals give different responses against the drugs or chemicals.

GENETIC MECHANISM

The units generating the heredity namely genes are located on chromosomes and they are parts of DNA molecules. Each of the gene pairs located on the same region of the chromosome are called "allele".

Because of genetic changes, enzymes, proteins and receptors of the individuals can be affected.

Affected enzyme's activity can be changes so that the metabolisms of the chemicals and drugs will be changed also. These changes in metabolism will cause the abnormal responses.

These abnormal responses are categorized in 2 groups:

1) Pharmacokinetic alterations
2) Pharmacodinamic alterations

RELATIONSHIP BETWEEN DOSE AND EFFECT

The base variations in the "regulator" and "promoter" regions arrangement cause polymorphisms. This is the main reason of individual differences or variations.

Variability

- It is the variation ability of living organisms.

Genetic Mutation, Genetic Polymorphism

Genetic Mutation: The changes formed in nucleotid sequencing of DNA molecule. Alterations and defects are occurred in genetic structure. Genetic mutations are kind of genetic polymorphisms. In order to be called as a mutation, the variation must be not more than 1% of the population.

Genetic Mutation, Genetic Polymorphism

Genetic Polymorphism: DNA sequence differences between individuals, groups or populations.
In order to be called as a polymorphism, the variation must be more than 1% of the population.

Polymorphism

- Existence of two or more different sequnce between the differnet individuals of the same species.
- They are thought to be come from the mistakes occurred during DNA replication.
- In human DNA, the 99.9% of the gene sequence look like the same.
- The genetic variations between humans arise from this 0.1% difference.

GENETIC VARIATIONS

- Single nucleotid polymorphisms (SNPs)
  1 SNP on each 300–1000 base pairs.
- Insertions/deletions (INDELS)
  This can be seen less frequently compared to SNPs, They are formed especially on the coding regions of the genes
- Copy number variations (CNVs) – big DNA segments (gene copying, gene deletions, gene reverse sequencing)

SINGLE NUCLEOTİD POLYMORPHISMS (SNPs)

- They are the single nucleotid changes at a spesific base position.
- They are the 85-90% of whole genetic variations.

SINGLE NUCLEOTİD POLYMORPHISMS (SNPs)

- In two different individuals, a difference is estimated in each 1250 bp (base pairs).

- It’s frequency is more than 1% percent in a population.

SINGLE NUCLEOTİD POLYMORPHISMS (SNPs)

PHARMACOKINETIC CHANGES

PHARMACOKINETIC (ADME)

PHASE I AND II REACTIONS IN DRUG METABOLISM

FACTORS AFFECTING DRUG BIOTRANSFORMATION

The most important enzyme group responsible from the metabolisms of drugs and other xenobiotics is CYP450 enzymes.

The alterations in CYP450 enzyme structures responsible from the Phase I reactions can change the effects of drugs and the other xenobiotics metabolized with these enzymes.

Cytochrom P450 (CYP450) enzymes

- 57 CYP450 gene

- CYP1, CYP2, CYP3 families enter the drug metabolisms

- These CYP enzymesplay a major role in 80% of the oxidative drug metabolism and 50% of the elimination of the well-known drugs (common drugs).

Human CYP450s and their contribution to hepatic drug metabolism

The phenotype of the drug metabolizing enzymes which of their structures or synthesis are destroyed is called slow metabolizer,

and the faster one is called fast metabolizer.

The alteration of the drug metabolism causes toxication or detoxification.

Human Polymorphic CYP examples

Example: The slow inactivation of isoniazid and similar drugs

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

This enzyme can not be induced. By genetic changes the enzyme’s level is decreased in some individuals’ livers but the type of the enzyme and its affinity to the substrate is not changed.

These individuals acetylise these drugs slowly. When they take these drugs, the plasma levels of the drug is higher than the ones who acetylise normally; because the elimination half life of the drug is prolonged.

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: Acatalasia

A rare hereditary metabolic disorder caused by lack of the catalase enzyme found in erythrocytes and tissues such as bone marrow, liver, blood cells and skin.

In Japan and Korea its frequency is 2 in 100000. Catalase catalyzes the reaction by which hydrogen peroxide is decomposed to water and oxygen. When you apply oxygen water to a

wound, due to no oxygen exit there won't be a foaming reaction if there is an acatalasia situation.

In some people by the effect of genetic reasons some enzymes are not found or found in an unusual structure. Therefore the rate of metabolism reactions related with these enzymes are decreased and the biological half life of the substrate is prolonged. The elimination speed decreases and due to the accumulation of the chemical the activity gets severe and toxic effects occur.

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 some individuals, the enzyme in plasma is in atypical form result in prolonged effect duration. Atypical enzyme's affinity to succinylcholine is low. The enzyme is produced in liver and controlled by 4 different genes.
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.

PHARMACODYNAMIC CHANGES

Several drugs and chemicals make different effects and toxicities in people with genetic disorders.

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

In hereditary methemoglobinemia, this enzyme is not existed in RBCs. Disease shows autosomal recessive hereditary and occurs only in homozygous individuals. These people are known to born with cyanosis.

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 hemoglobin

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.

Malaria drugs such as Quinine, Primacine, Pentacine
Analgesic antipyretic drugs such as Aspirin, Aminopyrine, Phenacetine, Propifenazone, Dipyron
Sulfonamids
Sulfones

Nitrofurantoine, Nitrofurazone, Furazolidone
Dimercaprol, Vitamin K, Probenecid,
cause hemolysis, in people with G6PD enzyme deficiency. Hemoglobin level decreases; urine gets black by hemoglobinemia and jaundice is seen as a result of haemolytic anemia.

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.

Some chemicals can bind with blood proteins, tissue components or enzymes so that they can longly stay in the organism. They don't leave the organism even they can be taken as a single dose. This is very important in drug toxicity. Patients who need to use the drugs that have accumulation property must be careful.

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.