

DRUG-GENE INTERACTIONS AND IMMUNE SYSTEM DISEASES
DRUG-GENE INTERACTIONS
DRUG
DRUGS...

With the effects they make in our body,

- Controlling the disease,
 - Supporting the therapy,
 - Stopping or relieving the symptoms,
 - Relieving our pains or
 - which makes it possible to protect from diseases
- they are natural, semi-synthetic or synthetic preparations that are given to living things by different application methods.

5 CORRECTS IN DRUG USE

- Correct drug**
- For correct person**
- In correct amounts**
- In correct time**
- In correct way**
(such as swallowing, chewing).

REASONS OF ADVERSE EFFECTS SEEN AFTER THE REGISTRATIONS THAT CANNOT
BE DETERMINED IN PRECLINIC AND CLINICAL STUDIES

2. Some adverse effects arise after a complex multi-factor process. It is not possible to detect them in experimental animal tests.

- The gene is the part of the DNA molecule that carries any of the inherited traits of living things, consisting of an average of 1500 nucleotides.
- Gene: Genes are a certain length of a DNA chain that is the smallest unit of genetic coding.
- DNA is formed by organic bases (Adenine-Thymine-Guanine-Cytosine), ribose sugar with five carbons and phosphate molecules.
- Genes are sequenced in this sequence according to the genetic code.

Base changes that may occur in the "regulator" and "promoter" region sequences of genes cause polymorphisms which are the main cause of individual differences

Variability

- The variation ability of the living organisms

Mutation

Changes or disruptions in the genetic structure of living things, namely chromosomes, DNA and genes.

GENETIC VARIATIONS



MUTATION

Rare variants in a population that occur **less than 1%**.



POLYMORPHISM

Its incidence in a population is **at least 1%**.

Polymorphism

- It is the presence of two or more different sequences between different individuals of the same genre.

- They are thought to have occurred as a result of errors during DNA replication.
- In human DNA, 99.9% of the gene sequence is similar.
- Genetic diversity among humans is caused by a difference of 0.1%.

Genetic Differences

- Differences in physical features
- Differences in susceptibility and resistance to disease
- **Differences in drug or food metabolism (DRUG-GENE INTERACTIONS)**

SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs)

- Single nucleotide difference occurred in a certain base position.
 - It accounts for 90% of all genetic variations.
- ### **SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs)**
- It is predicted that in human genome there are about 10-30 billion SNPs.
 - It is estimated that there is a difference of 1250 bp between two different individuals.
 - Its frequency in a particular population is usually more than 1%.

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

The structural differences in CYP450 enzymes responsible for Phase I biotransformation reactions change the effects of the xenobiotics metabolized by these enzymes.

Cytochrome P450 Isoforms:

- . CYP1A2
- . CYP3A

- . CYP2C9
- . CYP2C19
- . CYP2D6

The CYP3A family is a group of enzymes that are responsible for the metabolism of many drugs on the pharmaceutical market and have a risk of polymorphic changes.

CYP3A

- Calcium channel blockers
- Benzodiazepines
- HIV protease inhibitors
- Cyclosporine
- Non-sedative antihistamines

is responsible for the metabolism of many drug groups. They are found in GI tract and liver.

CYP3A Inhibitors

- Ketoconazole
- Itraconazole
- Fluconazole
- Cimetidine
- Clarithromycin
- Erythromycin
- Troleandomycine
- Amiodarone
- **Grapefruit juice**

CYP3A Inducers

- Carbamazepine
- Rifampin
- Rifabutin
- Ritonavir
- St. John's wort (hypericum)

The role of immune system in defence mechanism

- Immune system is evolved to protect living organisms against environmental pathogens (virus, bacteria, fungi, protozoa and multicellular parasites).
- For this reason, immune system is playing a major role in protection against infections.
- Immunity that provides control and elimination of infection is called protective immunity.

IMMUNE SYSTEM

IMMUNE SYSTEM ORGANS

1. Central Lymphoid Organs

- A) Bone marrow
- B) Thymus
- C) Bursa of fabricius and equivalent organs

2. Peripheral Lymphoid Organs

- A) Lymph Nodes
- B) Spleen
- C) **Mucosa-associated** Lymphoid tissues (MALT)

IMMUNE SYSTEM CELLS

- **I- Macrophages**
- **II- Lymphocytes**
 - B-lymphocyte Plasma Cell**
 - T-lymphocyte**
 - Th = T helper Lymphocyte
 - Tcy= T cytotoxic Lymphocyte
 - Ts = T suppresor Lymphocyte
- **III- NK = Natural Killer Cells**
- **IV- Other cells**
 - Neutrophil**
 - Eosinophil**
 - Bazophil and Mast Cells**
 - Trombocytes**

Immunostimulants

Metals (Ni,Be,Pt)

Penicillin

Sulphide, MSG, Tartrazine, Benzoate (Food additive and dyes)

Pyrethrins (Pesticide)

HCB,

Selenium

Immunosuppressors

1. Antineoplastics

Cyclophosphamide, Nitrogen mustard, 6-mercaptopurine, Azathioprine, Methotrexate, 5-fluorouracil, Actinomycin, Doxorubicin

2. Heavy Metals

Pb, Cd, Cr, CH₃Hg, NaOAs, ASO₃ etc.

3. Pesticides

DDT, Dieldrin, Carbaryl, Carbofuran, Methyl parathion, Maneb, Chlordane, HCB

Immunosuppressors

4. Halogenated Hydrocarbons

PCB, PBB, TCDD, Trichloroethylene, Chloroform, Pentachlorophenol

5. Polycyclic aromatic hydrocarbons

Anthracene, benzoanthracene, Benzo(a)pyrene, Dimethylbenzanthracene, Methylcholanthrene

6. Organic Solvents; Benzene, Toluene, Nitrobenzene, 2,4-dinitrotoluene, CCl₄

7. Others; DES, Glucocorticoids

Immunoglobulin structure

(Antibody)

Immunoglobulins:

- IgG : Defends against infection repeats.
- IgA : Especially found in secretions and protects mucosal membranes.
- IgM : Occurs at the beginning of the infection.
- IgD : The least immunoglobulin found in serum.
- IgE : Responsible for allergic and anaphylactic reactions. It plays role in defence against parasites.

Allergy

- It is the body's ability to react differently to certain nutrients, pollen, plants, animal hair, dust, insect bites and medicines.
- Allergic diseases are among the most common chronic pathological conditions worldwide.

CLASSIFICATION OF REACTIONS AGAINST DRUGS

I) Reactions independent of drug content

A. Psychogenic reactions

B. Coincidentally symptoms

II) Drug dependent reactions

A. Reactions in people who are not sensitive

B. Reactions in sensitive people

II) Drug dependent reactions

Reactions in people who are not sensitive;

1. Excess dose: Drug effects related with the concentration of drugs in the body.

Example; respiratory depression by the effects of the sedatives, hepatic failure with acetaminophen.

2. Side effects: Pharmacological effects formed with the normal drug doses. This side effects are the most common reactions occurred against the drugs.

Example; Tachycardia formation with epinephrine injection.

3. Seconder effects: Events that are only indirectly related to the primary pharmacological effect of the drug.

Example; Like the Jarisch-Herxheimer reaction caused by the release of microbial antigens and endotoxins after antibiotic treatment seen in some cases of syphilis treated with penicillin.

4. Drug interactions: Change in response to one or more drugs with the change of the patient's normal physiology.

Example; One drug causing enzyme induction to alter the metabolism of the other drug.

Erythromycin increases blood levels of theophylline / digoxin.

B. Reactions in sensitive people:

- **Intolerance:** Characteristic pharmacological effects, which occur with small doses of the drug in certain individuals. Like the formation of tinnitus after the use of a single aspirin tablet.
 - **Idiosyncrasy:** Formation of an unusual response to a drug different from its pharmacological effects. It happens only in sensitive individuals and does not include the immune mechanism. For example; Primakin causes hemolytic anemia in people with G6PD deficiency.
- 3. Allergy or hypersensitivity:** In some people, specific antibodies against the drug or its metabolites or sensitized lymphocytes (or both) are produced when the drug is encountered. REACTIONS CONTAINED ONLY WITH IMMUN MECHANISM CAN BE CLASSIFIED ALLERGIC.

General Features of Allergic Drug Reactions

- It occurs in a small part of the population and can also occur with low doses of the drug.
- No reaction occurs at the first contact with the drug.
- Often there is a latent period without any side effects after drug intake.

- Its clinical findings are not similar to the known pharmacological effects of the drug.
- With the use of the drug again, allergic symptoms occur again.
- With the cessation of the drug, symptoms usually subside within 3-5 days.
- Penicillins and sulphonamides are the most common drugs related with allergic drug reactions.

ALLERGIC DRUG REACTIONS

1) IMMUNOLOGIC CLASSIFICATION

- **TYPE I REACTIONS (Early type/anaphylactic)**
- **TYPE II REACTIONS (Cytotoxic)**
- **TYPE III REACTIONS (Immune complex)**
- **TYPE IV REACTIONS (Delayed type/cell mediated)**

2) CLASSIFICATION RELATED WITH ORGAN SYSTEMS

IMMUNOLOGIC CLASSIFICATION

TYPE I (EARLY TYPE / ANAPHYLACTIC) REACTIONS :

- **Anaphylaxia, urticaria and angioedema**
Penicillins anaphylaxia
- **Anaphylactoid reactions** (non-immunological origin) **Polymyxin, Aspirine and local anaesthetics.**

TYPE II (CYTOTOXIC) REACTIONS

- **Hematologic reactions:** Drug mediated Coomb's positive haemolytic anemia is the best example.
- **Interstitial nephritis:** Methicillin

TYPE IV (DELAYED TYPE / CELL MEDIATED) REACTIONS:

- **Contact dermatitis:** It occurs as a result of delayed hypersensitivity after topical

administration of drugs.

- **Acute pulmonary reactions:** Nitrofurantoin induced pulmonary fibrosis and gold therapy induced interstitial pneumonia.
- **Other reactions:** Drug induced interstitial nephritis, halothane induced hepatocellular damage.

OTOIMMUNE DISEASES

Immune tolerance

When the organism recognizes the antigen itself and does not react to them

It is called IMMUN TOLERANCE

That is

UNRESPONSIVENESS TO SELF ANTIGENS

Immune Tolerance

- 1) Central tolerance
 - Bone marrow B-cells
 - Thymus T-cells
- 2) Peripheral tolerance
 - Matured T-cells
 - Matured B-cells

Autoimmunity mechanisms theories

Clonal Deletion: It predicts that T and B lymphocytes that react to auto antigens are eliminated by sieving during the maturation period.

T Cell Supression In addition to the first two mechanisms, Ts cells are thought to secrete TGF- β 1 and suppress the immune system for a while.

Autoimmunity

- **5-7 % of adults are affected**
- **%5-8 in USA (100 miliard dollars/year)**
- **2/3 of women**
- **In 3rd position in industrialized countries**
- **In ages <80 disease is otoimmunity originated**
- **Can be seen at younger ages**

- **High risk in left-handed persons?**

Autoimmune disease mechanisms

- Immunological factors
- Genetic factors
- Infection agents
- Environmental factors
- Physiological factors
- Genetic Factors**

Familial predisposition

Being a woman

With specific HLA antigens

Ankylosing Spondylitis (HLA-B27)

Addison's disease (HLA-B8)

Rheumatoid arthritis (HLA-DR4)

Physiological Factors

Sex

Hormones

Stress

Pregnancy

Age (One of the main causes of death among women under 65)

The organism's reaction to its antigens is **Autoimmunity**

Antibody occurred **Autoantibody**

The disease developed **Autoimmune disease**

Autoimmune diseases

Organ specific Systemic

Organ specific autoimmune diseases

- Hashimoto's thyroiditis
- Autoimmune haemolytic anemia
- Autoimmune atrophic gastritis
- Goodpasture's syndrome
- Autoimmune thrombocytopenia

- Myasthenia Gravis
 - Graves disease
 - Insulin dependent Diabetes mellitus
- Systemic autoimmune diseases
- Systemic Lupus Erythematosus (SLE)
 - Rheumatoid arthritis (RA)
 - Sjögren's syndrome
 - Reiter's Syndrome
 - Systemic sclerosis
 - Poliarteritis Nodosa
 - Polymyositis-Dermatomyositis

Therapy Principles in Autoimmune Diseases

- Steroids
- Immune supressor drugs
- Autoantigen application
- Antibody application against **Cytokines** or other neuromediators

WHAT IS CYTOKINE?
CYTOKINE NETWORK
CYTOKINES AND INFLAMMATION
IF INFLAMMATION IS PERMANENT....
UNFORTUNATELY.....