

## PHARMACOGENETICS. VARIABILITY OF THERAPEUTIC RESPONSE AND PERSONALIZED MEDICINE

The recent great acquisitions generated along with the description of human genome provide the scientific base of individualized (personalized) medicine. For a short analysis of inter and intra – individual variability of drug response we will evoke very briefly to some data regarding the success rate in the pharmacological treatment of important diseases (as prevalence and seriousness) and the incidence of adverse events associated to the respective pharmacotherapy.

It is known from statistics and meta-analysis that the success rate in the pharmacotherapy of cancer, the therapy of neurologic and serious psychic diseases is situated between 30 and 60% (Paul Waring, Genetech), the majority not over passing 60 to 65%. From various reasons depending on patient, drug or monitoring, the lack of compliance to treatment increases the insuccess rate.

The secondary and adverse effects constitute a difficult burden for the world health systems. The drugs serious adverse events have a 6 to 7% contribution to the overall hospitalizations, an 2-3 days increase of hospitalizing duration and 100.000 deaths yearly in USA (Ingelman-Sundberg M., 2008).

In the period 1998 – 2005 the drugs adverse effects reported and the correlated deaths have increased around 2.7 folds (Th.Moore et al., 2007). In the process of new drugs promotion adverse effects are also observed, determining the withdraw of around 4% of overall new products, respectively in the period 1995-2005, 34 drugs have been withdrawn due to the hepatotoxic or cardiotoxic type of adverse effects (e.g.: cerivastatin, nefazodone, rofecoxib, terfenadine, tioglitazone and, recently, aprotinine).

Pharmacogenetics defines an inborn variability to drug response, phenomenon obvious in all forms of life, easily identifiable in bacteria or viruses (Kalow W., 1997). This variability can be illustrated, we think, very convincingly, by the Gaussian variability (distribution curve of variable response, observed in instances such as LD50 or ED50 determinations) which can be conceived as a resultant of inborn characters added with those induced by the impact with the environment, drug metabolism or its transport (transport, in a broad sense: absorption, distribution, efflux, elimination etc.). The response variability hints not only the inter-individual variability, but also the intra-individual variation, consequently to exposure to various environmental conditions, including drug treatment.

The intervariability represents a major concern in individual treatment assignment and extreme situation avoiding: the absence of therapeutic response or excessive response, serious adverse events etc.

Pharmacogenetics investigates and underlies the drug response interrelation with genetic variability, usually limited to a distinct variant (allele) of a target gene.

Pharmacogenomics studies the genome in a broad sense, respectively a large gene spectrum which may determinate response particularities to drugs.

The personalized medicine, the right dosage regimen for individual patient (Peck CC. & Cross JT., 2007), respectively, is based on each patient genotyping, identification of some genes variants and their correlation with the therapeutic response. There is already a database available (Hodge AE. et al, 2007), continuously enriching, allowing to define, but also to determine some biomarkers (Ingelman-Sundberg M., 2008) hinting the metabolism, multiple drug resistance, prevention of some major adverse events etc.

A case in point, there are 78 variants known of Cyp 2D6 associated with adverse events or lack of answer, including to some atypical antipsychotics. Many of the polymorphic genes code for inactive enzymes (see adverse events to risperidone) ( de Leon J. et al, 2005 and 2006; or ultrarapid activity variants, Voicu VA. et al, 2007).

It is foreseen the dose adaption for some antipsychotics or antidepressives based on the metabolism type, correlated with variants of cytochrome P450 2D6, 3A4 (Kirschheiner J. et al, 2005). The clinical studies relieve the significant correlation of some alleles coding for dopamine receptor D4, serotonin receptors 5-HT2A and 5-HT2C clozapine response in schizophrenia (Basile V. et al., Human Molec.Gen.,2002). The beginnings of pharmacogenetics and pharmacogenomics are mentioned (Ellenhorn MJ., 1997; Pirmohamed M., 2001) at one time with recognition by Pitagora of Vicia Faba seeds ingestion dangers („favism”) (510

B.C.), thereafter identified as a consequence of glucose-6-phosphate dehydrogenase (G6PD) deficiency as the mechanism of hemolytic crisis consecutive to food ingestion.

In a recent pharmacogenetics and pharmacogenomics brief historic, Pirmohamed M. mentions some important reference points.

The debut of the pharmacogenetics and pharmacogenomics scientific area is marked by the identification of heredity laws by Mandel in 1866. In 1906 Garrod A.E. publish in N.Y. „Inborn errors of metabolism”. Carson et al publish in Science (1956) a paper on G6PD enzymatic deficiency consequences on erythrocytes (expose to primaquin), followed immediately by the publication by Motulschi AG. in JAMA (1957) of a paper on drug effects correlations with their metabolism inborn defects.

In 1957 Kalow W. and Genest K. publish in Can.J.Biochem.Physiol. the detection method of atypical forms of human pseudo-cholinesterase and describe the parameter called „dibucaine number”, still actual. A step forward in some drug metabolism genetic variability identification was the characterization of acetylation polymorphism, the target being the isoniazid administered to humans.

W.Kalow publishes in 1962 „Pharmacogenetics – heredity and the response to drugs”. Between 1977-1988 (Mahgoun et al., Eichelbaum et al., Gonzales et al.) discover and characterize the debrisoquin-hydroxylase, thereafter identified and called as cytochrome P450 2D6. Remarkable contributions on Cyp 2D6 characterization of Cyp 2D6 were brought by the clinical pharmacology schools from Sweden (Sjokvist F., Bertilsson L., Steiner et al.) and Spain (Benitez et al).

The 1988-2000 period includes progresses in polymorphism identification for genes coding for metabolism phase I and II enzymes, including the efflux pumps; this period ends with the historical success of 2000 human genome study. The scientific consequences of these acquisitions is more and more evident, currently their application concerns hinting also the **translational medicine concept**, intensifying the fundamental scientific data transfer into medical practice, respectively.

The genetic polymorphism is usually considered manifest in about 1% of the population, consisting in some instances in one amino acid sequence alteration within one protein correlated with the gene function alteration. For exemplification, we mention some aspects of some genes polymorphism coding for the enzyme in drug disposition phase (metabolism, transport, distribution), respectively:

- Cyp 2C9 (variant) can code the response decrease or absence to warfarin or, otherwise, induce hemorrhagic events; increase of phenytoin toxicity or tolbutamide dose decrease **necessity**;
- Cyp 2D6 – increase of codeine adverse events (ultra-rapid metabolizer variant) or decrease or absence of codeine effects (7% of Caucasians – poor metabolizers);
- P Glycoprotein – digoxin blood concentration and effects **alteration**;
- N-acetyl-transferase – variants: poor acetylators produce the increase of lupus erythematosus risk to procainamide or appearance of toxic effects to isoniazid;
- Thiopurin-methyl-transferase, poor metabolizers variant – may induce medullar aplasia to 6-mercaptopurine or azatioprin, and rapid metabolizers variant – poor therapeutic effect;
- Pseudocholinesterase – reduce activity variant, produces prolonged apnea to succinylcholine;
- UDP-glucuronil-transferase – decrease activity variant – increases the irinotecan toxicity;

It is to be mentioned in fact that the interindividual genomic variance is focused on 0,1% from human genome, making each individual an unique entity.

In other words two different persons have in common 99,9% from the DNA sequence and differ by 0,1%.

Single nucleotide polymorphisms (SNP), unlike mutations, represent genetic variability loci where the least common alleles (gene variants) are represented in 1% of the population. The human genome contain about 10 millions SNP's.

Applying the genotyping procedure to some patient categories is possible, but currently very limited. Which is the explanation? In SUA, by FDA decision, a number of around 10% of approved drugs contain pharmacogenomic information in the leaflet. The biomarkers intended to potentially identify the therapeutic response, to identify the risks, to guide the dose selection, all the respective drug potential polymorphic targets etc. are either **mandatory, recommended or informative**. From the mandatory ones we mention: EGFR expression (presence or absence of epidermal growth factor Receptor expression) in squamos cells cancer at lead or throat level, colorectal cancer. Targeted drugs: cetuximab, gefitinib.

- over expression of Her2 neu-detection of HER2 protein presence; overexpressed for patient in trastuzumab treatment for breast cancer (Herceptin®)

We mention some recommended biomarkers test: Thiopurin-methyl-transferase deficiency (TPMT); targeted drugs: mercaptopurin, azathioprin and thioguanin. Also tests for reduced activity allele of UDP-GT (UGT1A\*28) amplifies neutropenia risk in irinotecan treatment.

Concerning informative test we mention:

- Cyp 2C9 variants – poor metabolizers;
- Cyp 2D6 variants – poor metabolizers;
- G6PD deficiency;
- N-acetyl-transferase variants (slow or poor metabolizers).

What are the hopes regarding individualized therapy in next future?

The main targets will be:

- Defining potential characteristics of Cyp 450 polymorphism (populational samples);
- Implementation in selected clinical units (centers for excellence) of some current tests, correlated with the therapy type;
- Evaluation of personalized therapy consequences, in the therapeutic response and/or adverse events and so to increase the therapeutic success rate and reduce the intensity and frequency of adverse events.

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