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# **PLENARY LECTURES**

## Adverse drug reactions and personalized medicine

S. Yanev

Department of Drug Toxicology, Institute of Neurobiology, BAS, Sofia, Bulgaria

**Introduction** Adverse drug reactions (ADR) can be defined as, “an unwanted or harmful reaction experienced following administration of a drug, or combination of drugs, *under normal conditions of use* and is suspected as being related to the drug (or combination)”.

In general they can be divide into two main groups: type A (predictable, linked to the main pharmacological effect) and type B (unpredictable, idiosyncratic, non-connected with the main pharmacological effect (Table 1).

**Table 1** Classification of ADR

	Type A	Type B
Pharmacology	Qualitatively normal Quantitatively abnormal	Qualitatively abnormal
Predictability	Yes (usually)	No (usually)
Drug-dependence	Yes	No (usually)
Frequency	Common (usually)	Rare (usually)
Seriousness	No (usually)	Yes (often)

We can further divide ADR in type C (associated with long-term use, involves dose accumulation; example: phenacetin and interstitial nephritis); type D (delayed effects like carcinogenicity, teratogenicity, dose independent; example: fetal hydantoin syndrome); type E (withdrawal reactions); type F (failure of therapy).

The current classification is defined only by properties of the drug – its known pharmacology and the dose dependence of its effects. A modern view of development of ADR also includes properties of the reaction (the time course of its appearance and its severity) and properties of the individual (the genetic, pathological, and other biological differences that confer susceptibility). That is the three dimensional classification system based on dose relatedness, timing, and patient susceptibility (DoTS) proposed by J.K.Aronson and R.E.Ferner (BMJ, 2003, 327, 1222–1225).

Adverse drug reactions (ADRs) often arise because of the formation of metabolic intermediates. Our knowledge of the drug metabolizing systems showed that they have a high level of genetic variation. When those variations are present in individuals taking more than one drug the chance of having an adverse drug reaction is greatly increased.

In this presentation, the mechanisms of some adverse drug reactions are described based on different genotype and phenotype of drug metabolizing systems and pharmacological targets (enzymes and receptors).

**Discussion** In general, we can divide drugs in two groups, depending of the way by which the reactive metabolites induced ADRs – those of which possessed intrinsic toxicity and those induced metabolic idiosyncrasy. The first group induced impairment of cellular metabolism and calcium homeostasis; oxidative stress and lipid peroxidation; bind covalently to different cellular macromolecules; developed cell apoptosis and necrosis.

Many factors, including genetic, environmental, in uterus exposure, life style, diet, drugs and eating habits leave a “metabolic signature” and contribute to a “metabolic fingerprint map” unique for each individual organism. This fact could explain why after the same drug dose two different persons react different, with development of ADR or some times of drug failure.

### I. Genetic polymorphism, drug metabolism and ADR (type A)

From the top 27 drugs frequently cited in ADR reports 59% (16/27) metabolized by at least one enzyme having poor metabolizer (PM) genotype and 38% of them are (11/27) metabolized by CYP 2D6

Here are some examples of drugs metabolized by enzymes with variant alleles associated with poor metabolism and implicated in different ADRs:

- CYP1A2 (typical antipsychotics and tardive dyskinesia);
- CYP2C9 (Warfarin /haemorrhage/, Tolbutamide /hypoglycaemia/, Phenytoin /skin toxicity/);
- CYP2C19 (Mephenytoin /neurotoxicity/, Diazepam /prolonged sedation/); Omeprazole and Lansoprazole /higher therapeutic response/.

CYP2D6 (Antiarrhythmics /arrhythmias/,  $\beta$ -Blockers /bradycardia/, Tricyclic antidepressants /confusion/, Opioids /protection from oral opiate dependence/, Phenformin /lactic acidosis/, Perhexilene /hepatotoxicity/); codeine /poor analgesic efficacy/; tramadol /poor analgesic efficacy/.

- CYP3A4 (Anti-leukaemic agents /treatment-related leukaemia/);
- plasma butyrylcholinesterase (Succinylcholine /prolonged apnoea/);
- N-acetyltransferase (Sulfonamides /hypersensitivity/, Amonafide /myelotoxicity/, Procainamide, hydralazine, isoniazid /lupus/);
- thiopurine methyltransferase (6-Mercaptopurine, azathioprine /myelotoxicity/);
- dihydropyrimidine dehydrogenase (5-Fluorouracil /myelotoxicity/);

UDP glucuronosyl transferase 1A1 (Irinotecan /diarrhoea, myelosuppression/).

Increased risk of toxicity or failure to response can be found in patients with extensive expression (EM) of CYP 2D6 as:

- codeine (morphine toxicity);
- encainide (possibly proarrhythmias)
- nortriptyline (poor antidepressant efficacy at normal doses);
- propafenone (poor antiarrhythmic efficacy at normal doses);
- tropisetron and ondansetron (poor antiemetic efficacy at normal doses)

In some cases, the appearance of selective organ toxicity by some drugs can be explained by their metabolic activation to reactive, toxic metabolite (s):

- paracetamol (liver and kidney toxicity)
- amiodarone (o<sub>2</sub>, lung and skin toxicity)
- valproic acid (reye-like syndrome)
- isoniazid (polyneuritis)
- furosemid (pancreatitis)
- nitrofurantoin (lung toxicity)
- cimetidine (liver toxicity)

- diclofenac (liver toxicity)
- ranitidine (liver toxicity)

## II. Genetic polymorphism of therapeutic target – enzyme or receptors

There are many examples of genetically determined different pharmacodynamic response or ADR due to defective pharmacological target (enzyme) as:

- Glucose-6-phosphate dehydrogenase deficiency – hemolytic anemia after antimalaric drugs;
- Thiopurin S-methyltransferase deficiency – toxic effects after azathioprine in treatment of leukemia and autoimmune diseases;
- ALOX-5 (5-lipoxygenase) - asthmatic patients who carry mutations of the core promoter of 5-lipoxygenase (ALOX-5) respond poorly to ALOX-5 inhibitors such as Zileuton;

ACE – ACEDD-genotype has two times higher maximal velocity and 1.5 higher concentration in the body compared with the wild ACEII-genotype, thus lead to dramatic differences in therapeutic effects of ACE-inhibitors.

There are many ADR or therapeutic failure due to defective pharmacological target (receptors) as:

- Serotonin transporter (5-HTT) gene is reportedly a determinant of response to fluvoxamine, a selective serotonin re-uptake inhibitor (SSRI);
- Arg16/Gly16 or Gly16/Gly16 variants of b2-adrenoceptors have been display a much less favourable immediate bronchodilatory response to salbutamol;
- Patients with homozygote mutation Gly17Arg of beta-2 adrenoceptor exerted increased asthmatic outburst after treatment with “normal” doses of albuterol;
- Mutation of Apolipoprotein E (*ApoE4*) gene leads to decreased response to tacrin in treatment of Alzheimer disease;
- P-glycoprotein (MDR) mutation – abolished the effectiveness of alkylating chemotherapeutics because of their increased excretion out of cancer cells;
- Patients with Ryanodine receptors mutation in skeletal muscles are exposed to malignant hypothermia after anesthesia with halothane;

Single point mutation in serotonin receptor leads to great variability in effectiveness of sumatriptan.

## III. Immune-mediated drug toxicity (ADR type B)

Requirement for development of the immune response to certain drug is appropriate hapten formation in the body through:

### 1. Direct haptenization (penicillin, penicillamine, captopril)

- The clinical sings of most common hypersensitivity reaction to drugs are:
- Anaphylaxis – type I reaction after betalactame antibiotics, NSAID, sulfonamides;
- Hemolytic anemia – penicillin, cephalosporin, methyl-DOPA, nomifensin;
- Agranulocytosis – aminopyrin, levamisol, captopril, mianserin, propylthiouracil, penicillin-G, sulfasalazin, sulphmetoxazol);

Skin reactions – trimetoprim, anticonvulsants, cephalosporin, penicillin).

2. On the other hand, there are many drugs known to cause *immune-mediated toxicity*, which undergo bioactivation by different cytochrome p450 isoforms. Most of them are mechanism-based inactivators, which reactive metabolites covalently bind to the corresponding CYP protein. By still not fully understood mechanism, organism develops antibodies against this complex. The consequence of this is the appearance of different immune mediated organ toxicities, like:

hepatotoxicity (dihydralazine /CYP1A2/, halothane and ethanol /CYP2E1/, phenytoin /CYP2C9/, tienilic acid /CYP2C9/, sulphamethoxazole and carbamazepine /CYP3A4, CYP2C9/;

skin toxicity (sulphamethoxazole, carbamazepine, phenytoin).

3. Metabolism of drugs by activated leukocytes (NADPH oxidase and myeloperoxidase) leads to:

- skin reactions; agranulocytosis (lupus) – sulfamethoxazole, dapson, propylthiouracil, levamisole, ticlopidine, clozapine, 5-aminosalicylic acid, procainamide, mianserin.

**Conclusion** The main goal of contemporary personalized medicine is to find the *right* dose of the *right* drug for the *right* indication for the *right* patient at the *right* time. This approach should decrease drastically in the future the incidences of adverse drug reactions. A broad spectrum of our society could contribute for the success of this goal.

The important role of different participants in drug synthesis and usage to decrease the incidences of ADRs could be described as follows:

Producers – to perform directed synthesis of new compounds;

Scientists – to find new markers for testing gene and phenotype polymorphism and adverse drug reactions;

Teachers - to train knowledgeable clinical pharmacologists and pharmacists;

Centrum for ADR – to do better analysis of the signals for ADR and spreading of the information;

Physicians and pharmacists - to achieve individualization of the pharmacotherapy;

Patients – to have better information and less self-medication.