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Bulletin on Adverse Drug Reactions

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Committee Members for Bulletin on Adverse Drug Reactions

Lokmanya Tilak Municipal Medical College & General Hospital, Mumbai.

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From the Editor's desk

Dear Friends and Colleagues

It gives me great pleasure to present to you the second issue of "Bulletin on Adverse Drug Reactions".

You are all aware that the first issue was inaugurated by Dr Y K Gupta, Coordinator, Pharmacovigilance Programme Of India at the 17th Annual Meeting of SRS.

Our efforts in field of pharmacovigilance was well recognized by all and I am happy to announce that our prestigious institute has now been included as one of the pharmacovigilance centre in India.

I believe it is another feather in the cap that out institute is recognized at the national level for Pharmacovigilance and it could never be possible without the direct and indirect support of all the clinical departments of our institute who contributed to the activity of Pharmacovigilance.

It also give me great pride to inform that this bulletin which was first intended for circulation only in our institute is now circulated to all the leading medical colleges in India as per the recommendations of respected Dean Madam.

The outcome of this activity has been very rewarding. We are not only getting words of appreciation from all the places but also back at home our ADR reporting from the clinical departments has doubled since the last issue.

I would like to request all the departments to continue their support to ADR reporting and also contribute to the bulletin in the form of case reports or articles.

Finally, I would also like to thank all the members of Department of Pharmacology who worked wholeheartedly to bring to you this issue of the bulletin on ADR.

Thank you

Dr Sudhir Pawar

PHARMACOGENOMICS OF ADVERSE DRUG REACTIONS

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Introduction

Adverse drug reactions (ADRs) are a significant cause of morbidity and mortality. On the basis of preventability, these adverse reactions have been classified as preventable and non-preventable. Some of the non-preventable ADRs have a genetic basis in their causality and can be prevented with the help of knowledge of Pharmacogenomics. [1]

Pharmacogenomics involves genome-wide analysis of the genetic determinant of drug efficacy and toxicity (Figure 1).[2] The two arms of pharmacogenomics are drug efficacy and drug toxicity. Here we discuss the potential role and applications of pharmacogenomics in predicting and preventing drug toxicity/ADRs.

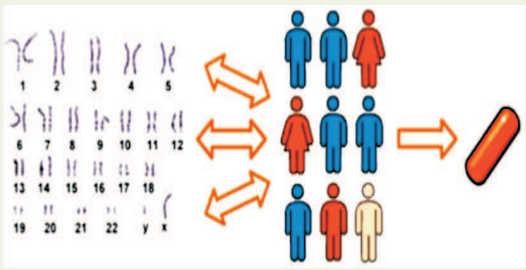

Fig 1: Pharmacogenomics –Genome wide analysis

Need of pharmacogenomic testing

The genetic constitution of population is varied. In a given population, the response of individuals will vary in response to different drugs. Majority may have full response, some will be having partial response, some may not be responsive and few may have susceptibility to serious ADRs depending on the genetic variability. Thus there exists the need of pharmacogenetic testing to individualize the therapy and avoid possible serious ADRs.

Genetic basis of ADRs

Genetic variations can be single nucleotide polymorphism (SNPs), gene deletion polymorphism; copy number variant (CNV) or variable number tandem repeats polymorphisms.[2] Adverse reactions in an individual can be due to genetic variations in genes for drug-metabolising enzymes, drug receptors, and drug transporters (Figure 2).[3]

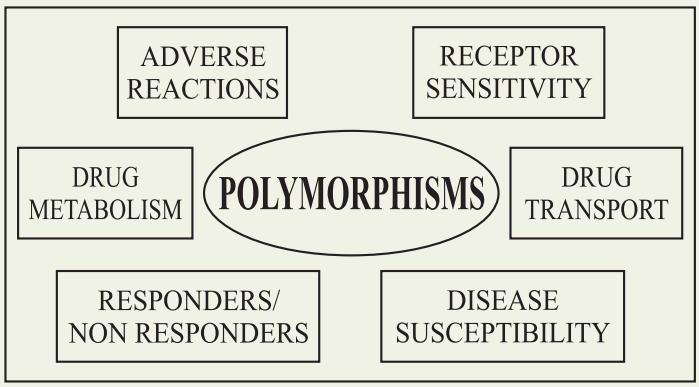

Fig 2: Effects of polymorphism

1. Genetic variation in drug metabolizing enzyme

The genetic variation in drug metabolizing enzymes has been amongst major factors in determining susceptibility to ADRs. The metabolizing status of an individual can be as an ultra-rapid metabolizer (UM) and poor metabolizer (PM) depending on genetic variability in drug metabolizing enzymes. For example, gene deletion polymorphism in CYP2D6 results in null enzyme activity and the individual is a poor metabolizer. The copy number variant polymorphism (extra copies of gene) in CYP2D6 results in increased capacity of metabolism and individual is a rapid metabolizer. The drugs affected by CYP2D6 include SSRIs, tamoxifen, codeine, β-blockers. [2, 3] Given the metabolizer status, the efficacy and toxicity of these will vary in an individual (Figure 3).

Another example is of oral anticoagulant warfarin which is metabolized by the enzyme encoded by gene cytochrome P4502C9 (CYP2C9). SNP in this gene results in commonly encountered variants CYP2C9*2 and CYP2C9*3 which have 12% and 5% of the enzyme activity, respectively. [4] Thus metabolism of warfarin is reduced with increased risk of bleeding including serious bleeding events and other complications. The population prevalence varies with 3 – 20% in Caucasians and 1 – 4% in Asians and American Africans. [2, 5]

The polymorphism of an enzyme Thiopurine methyl transferase (TPMT) which metabolizes immunosuppressant 6-mercaptopurine (6MP) results in reduced enzyme activity with 6MP toxicity i.e. myelosuppression. [2, 6] Other thiopurine analog azathioprine can also be affected. [2]

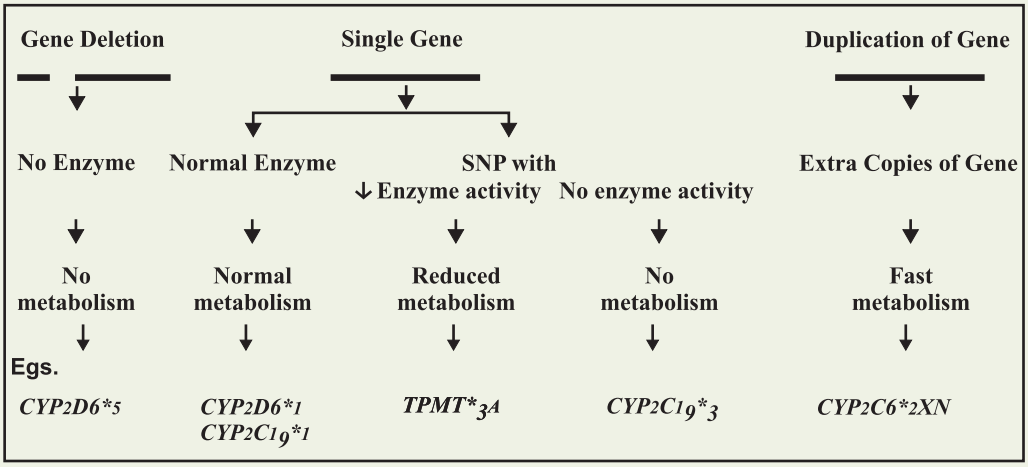

Fig 3: Diagrammatic representation of genetic variations that may affect drug metabolism.

2. Genetic variation in drug receptors

The most studied genetic variations as regards to drug receptors is β_2 adrenergic receptor (ADRB2). The most studied SNPs are Arg16Gly, Gln27Glu and Thr164Ile. The Gly16 alleles predisposes individual to nocturnal asthma and have decreased response to beta-agonist therapy (albuterol). [3, 7]

Mutation on five genes coding for cardiac ion channels (LQT 1 - 5) resulted in sudden cardiac death due to long QT caused by drugs like anti-arrhythmics and other drugs which also tend to prolong QT interval. [6] Other receptors shown to be genetically polymorphic with possible alterations in clinical phenotype include G-proteins, Angiotensin-II receptor, Angiotensin converting enzyme, α-2 receptor, Dopamine D_4 receptor, endothelial NO synthase, $5HT_4$receptor.

3. Genetic variation in drug transporters

The efflux pump identified in various tissues is P-glycoprotein. The mutated variant for the multidrug resistance gene, MDR1, which codes for P-glycoprotein, may alter its function. Function of P-glycoprotein is to export substances from inside the cell to outside. Its mutation affects its substrates which include chemotherapeutic agents, cyclosporine A, digoxin, verapamil, most HIV-1 protease inhibitors etc. The concentration of digoxin was elevated four times in person homozygous for mutation in MDR1. [3] Similarly, other drugs can get affected causing elevated concentration in plasma and more toxicity.

Other genetic markers for adverse reactions

Many of the adverse drug reactions have immunological basis in their causation. For immune-mediated toxic effects, much focus has been placed on the major-histocompatibility-complex (MHC) class I genes. Amongst the identified genomic markers, highest specificity is seen among the HLA allelic variants. [8]

The examples include HLA-B*5701 polymorphism responsible for abacavir induced hypersensitivity, HLA-B*1502 polymorphism resulting in increased risk of carbamazepine induced Stevens-Johnson syndrome and toxic epidermal necrolysis. [5,8] HLA-B*1502 allele is present in 100% of carbamazepine-induced Stevens - Johnson syndrome cases and is more common in Asians than in other races. [2,5] Both abacavir and carbamazepine should be avoided in individuals having these polymorphisms in HLA.

Methods for Pharmacogenetic testing

These include

- PCR with mutation-specific endonuclease
- PCR and allele-specific hybridization
- Oligonucleotide chip hybridization
- Laser lithography - guided oligonucleotide chip hybridization
- Rapid throughput pyrosequencing
- Taqman probe screening
- Genome wide SNP array

AmpliChip

The approval of world's first microarray based pharmacogenomic test has been called a "milestone" in personalized medicine. [9,10] It tests for genetic variations in two common drug metabolizing enzymes CYP2D6 and CYP2C19 which metabolize majority (25%) of prescription drugs. [10]

For CYP3A4 which metabolizes more than 50% drugs, 39 allelic variants of the CYP3A4 gene have been described. However, functional characterizations of most CYP3A4 variants reveal a limited impact on protein expression or activity. [11]

Current trends

Currently there are only few pharmacogenomic tests that are used or recommended clinically. A survey of FDA-approved labels of drugs approved from 1945 to 2005 found that 69 labels contained information associated with human genomic biomarkers. [12] Despite great interest, the use in clinical practice is slow. A major challenge to its adoption is the current lack of evidence about their clinical utility and how to use the tests in clinical practice. [9] The genetic variations that have been established and are recommended for testing in clinical setting are given in table 1.

Table 1 : Genetic variations and adverse effects due to drugs

Drug	Genotype involved	Clinical Effect
Warfarin	CYP2C9 and VKORC1	Drug toxicity with increased bleeding events
Irinotecan	UGT1A1	Increased risk of Neutropenia
Codeine	CYP2D6	May result in fatal side effects in nursing babies
Tamoxifen	CYP2D6	Poor or ultra-rapid metabolizer phenotype, Drug toxicity and poor efficacy will result with respective phenotype
Trastuzumab	HER2	Drug should be given if tested positive for genotype
Azathioprine	TPMT	Myelosuppression; Drug should be given at lower doses or should be discontinued in case of toxicity
Abacavir	HLA-B*5701	Hypersensitivity, Drug should not be given if tested positive for the genotype.

Table 2 gives the different genetic variations some of which have been established in few numbers of studies and require further confirmation from large population studies.

Table 2 : Other genetic variations and their association with drugs [3, 13, 14]

Drug	Genotype involved	Risk / Clinical effect
Antipsychotics	HTR2A	Susceptibility to tardive dyskinesia
Methotrexate	MTHFR	Increased toxicity
Succinylcholine	BCHEA	Prolonged apnoea
Cisplatin	GSTM3*3A	Increased risk of ototoxicity
Anti-tubercular (INH)	NAT2 (Slow acetylator)	Increased risk of drug induced lupus
Fluorouracil	Dihydropyrimidine dehydrogenase	Neurotoxicity, myelotoxicity
Diazepam	CYP2C19	Prolonged sedation
Phenytoin	CYP2C9	Phenytoin toxicity
Amoxicillin–clavulanate	HLADRB1*1501	Hepatitis
Clozapine	HLA-B38, DR4 and DQ3	Agranulocytosis
Hydralazine	HLA-DR4	Systemic lupus erythematosus
Levamisole	HLA-B27	Agranulocytosis
Oxicam	HLA-A2 and B12	Toxic epidermal necrolysis

Conclusion

Pharmacogenomics holds the promise to reduce the burden associated with non-preventable, genetically determined adverse drug reactions. The current problems in adoption of pharmacogenomics will soon be overcome. The advent of pharmacogenomic techniques to supplement clinical diagnosis gives promising advancement towards personalized management of ailments in an individual.

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SUMMARY OF ADRs IN LTMMC & LTMGH
(April 2011 to July 2011)

SR. NO	REACTIONS	SUSPECTED DRUG	WHO CAUSALITY	CASE REPORTS IN LITERATURE
1.	Encephalopathy	Methotrexate	Probable	Well Documented
2.	Pseudotumour Cerebri	Vitamin A	Probable	Well Documented
3.	Rash	Vancomycin	Probable	Well Documented
4.	Thrombocytopenia	Rifampicin	Probable	Well Documented
5.	Toxicity	Drug Interaction between Warfarin and Diclofenac/ Paracetamol	Possible	Well Documented
6.	Rash	Ibuprofen	Probable	Well Documented
7.	Fixed Drug Eruption	Co-trimoxazole	Probable	Well Documented
8.	Hematuria & per Rectal Bleeding	Warfarin	Probable	Well Documented
9.	Accidental poisoning, Toxicity & Death	Methotrexate	Possible	Well Documented
10.	Steven-Johnson Syndrome	Carbamazepine/ Lamotrigine	Possible	Well Documented
11.	Aseptic Meningitis	Bupivacaine	Possible	Well Documented
12.	Hypoglycemia	Ringer's Lactate/Propofol/ Ketamine/ Midazolam/ Ranitidine/ Ondansetron/ Fentanyl	Unclassifiable	Cannot be commented
13.	Tachycardia	Propofol/ Ketamine/ Ringer's Lactate	Possible	Well Documented
14.	Hypoglycemia & Seizures	Glimepiride / Metformin/ Pioglitazone	Possible	Well Documented
15.	Hypoglycemia	Unknown Oral Hypoglycemic Agent	Unclassifiable	Cannot be assessed
16.	Hepatitis	Rifampicin/ Isoniazid/ Pyrazinamide	Possible	Well Documented
17.	Abdominal pain, Vomiting & Giddiness	Efavirenz	Possible	Well Documented
18.	Hypoglycemia	Glibenclamide/ Metformin/ Pioglitazone	Possible	Well Documented
19.	Hyponatremia	Hydrochlorothiazide	Probable	Well Documented
20.	Nausea & Vomiting	Stavudine/ Nevirapine/ Lamivudine	Possible	Well Documented

SR. NO	NAME OF REACTION	SUSPECTED DRUG	WHO CAUSALITY	CASE REPORTS IN LITERATURE
21.	Rash	Artemether/ Lumefantrine	Possible	Well Documented
22.	Rash	A.S.V. Serum/ Metronidazole/ Cloxacillin	Possible	Well Documented
23.	Rash, Nausea,	Unknown Drug (? Chloroquine)	Unclassifiable	Cannot be assessed
24.	Hepatitis	Isoniazid/ Rifampicin/ Pyrazinamide	Possible	Well Documented
25.	Hypoglycemia	Glibenclamide/ Metformin	Possible	Well Documented
26.	Steven-Johnson Syndrome	Isoniazid/ Rifampicin/ Pyrazinamide/ Ethambutol/ Streptomycin	Possible	Well Documented
27.	Cardiac Arrest	Pentazocine/ Ondansetron/ Tranexamic acid/ Pentobarbitone/ Succinylcholine	Unclassifiable	Cannot be Commented
28.	Thrombocytopenic Rash	Unknown Drug	Unclassifiable	Cannot be Commented
29.	Rash	Doxycycline/ Choroquine/ Paracetamol	Possible	Well Documented
30.	Rash, Altered sensorium & Death	Metronidazole/ Ciprofloxacin/ Doxycycline/ Ceftriaxone	Rash- Possible Altered sensorium- Unclassifiable	Rash- Well documented Altered sensorium & Death- Cannot be Commented
31.	Steven-Johnson syndrome progressing to Toxic Epidermal Necrolysis	Nevirapine/ Stavudine/ Lamivudine	Possible	Well Documented
32.	Fixed Drug Eruption	Norfloxacin/ Tinidazole	Possible	Well Documented
33.	Macular Rash	Co-trimoxazole	Probable	Well Documented
34.	Toxic Epidermal Necrolysis	Phenytoin	Probable	Well Documented
35.	Rash	Levofloxacin/ Azithromycin	Possible	Well Documented
36.	Raised Liver Enzymes	Isoniazid/ Rifampicin/ Pyrazinamide	Possible	Well Documented
37.	Rash	Cefoperazone	Probable	Well Documented
38.	Rash	Ciprofloxacin/ Tinidazole	Possible	Well Documented
39.	Rash	Ofloxacin/Ornidazole/Paracetamol Albendazole/ Pantoprazole	Possible	Well Documented