Different people respond differently to the same drug. It is well known that this difference in drug response is because of genetic differences.

The study of these genetic differences to predict drug response is called Pharmacogenomics.

According to pharmacokinetics and genetics there are four types of people:

- 60 percent of the population will respond positively to a drug.
- 25 percent of the population is fast metabolisers of the drug and it means that the drug will get washed out of the body, before it can have any positive effect.
- 10 percent of the population is slow metabolisers. People in this population will have minor or major side effects because of accumulation of the drug, as the drug gets washed out very slowly.
- Five percent of the remainder population shows undetectable or no enzyme activity and so all the drug taken in by the person keep accumulating and this can cause severe side reactions.

In the U.S. alone, 20 million people need hospitalization to recover from these drug induced reactions and close to 1 lakh people die every year.

It is alright if a mild drug for headache or fever does not work, but strong drugs like chemotherapy can cause severe damage, if they accumulate.

Doing a genetic test can give lots of information on how a patient is going to respond to drugs; so appropriate drugs and their dosage can be arrived at.

This subject is called Pharmacogenomics.

Tests Available Today!

**Docetaxel (CYP3A4)**

Docetaxel displays a broad spectrum of antitumor activity, and activity against breast, head and neck, lung, ovarian and prostate cancer. An important draw back with the use of docetaxel is the large inter-individual variability in efficacy and toxicity. Adverse effects of Docetaxel include alopecia, asthenia, dermatological reactions, fluid retention, hypersensitivity reaction, motor and sensory neuropathies, stomatitis and diarrhoea. Docetaxel is extensively metabolized by cytochrome P450 3A4 to yield an inactive oxidation products. Variant alleles of CYP3A4 are common in our population, which results in decreased enzyme activity and increased toxicity. CYP3A4 is the most popular candidate for a genotyping test that would predict the potential for toxicity and allow individualized dose adjustments to be made.

### Pharmacogenetics: A Case Study

**Warfarin (CYP2C9 and VKORC1)**

Different patients need different doses of warfarin to attain the desired Prothrombin Time (PT) / INR. This difference can be attributed to diet, other co-administered drugs, age, sex, weight etc. But, sometimes two patients having very similar attributes might need very different doses of warfarin. This inter patient variation has been a hot topic of research in genetic laboratories and finally, US FDA has asked the pharma companies to modify the package insert and to mention that patient having mutations in CYP2C9 and VKORC1 are at...
A committee (Vatis et al.) offers a nomenclature for NAT allogenes.

Johansson Ingelman-Sundberg and Bertilsson discover that Stable gene amplifications of CYP2D6 cause the uttarapid metabolizer phenotype.

Heim and Meyer publish the first allele specific pharmacogenetic gene test for CYP2D6 (Ref. 38).

First nomenclature of the P450-supergene family.

Blum, Grant and Meyer purify N-acetyltransferase 1/2 (NAT 1/2) and done the respective genes as well as the mutations of NAT2 that cause the acetylation polymorphism.

PCR allows genetic sequences to be amplified exponentially.

Discovery of the genetic polymorphism of thiopurine-methyltransferase (TPMT) by Weinshilboum and Sladek.

(1967–1973) Sjöqvist and his co-workers establish that the metabolism of tricyclic antidepressants is under genetic control.

Evans establishes the genetic control of isoniazid acetylation.

Metabolism conceptualizes that inheritance might explain many individual differences in the efficacy and toxicity of drugs.

Kalow and Staron characterize serum cholesterol esterase deficiency in a subject with succinylcholine apnea.

(1957–1970) Twin studies indicate polygenic influences on the pharmacokinetics of numerous drugs.

The first issue of the journal Pharmacogenetics is published.

association of primaquine-induced hemolysis with glucose-6-phosphate dehydrogenase deficiency in erythrocytes.

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a greater risk of severe bleeding. These patients need much lower dose depending on the type of mutations they carry. Now, there are internationally accepted clinical guidelines to select the right dose for every patient and hence, avoid severe bleeding from Warfarin.

Irinotecan (UGT1A1)

Irinotecan has been a valuable drug as first line therapy especially for gastrointestinal malignancies. Irinotecan is a prodrug and must be converted to SN-38 to have cytotoxic activity. Once a dose has done its job, the drug needs to be detoxified and cleared from the body. The enzyme responsible for this reaction is UGT1A1. Mutations in UGT1A1, lead to lower enzyme activity. There are retrospective studies, and prospective pilot studies with solid tumor treated with Irinotecan, where severe diarrhoea and neutropenia was observed only in patients with UGT1A1 *28 mutation. Severe toxicities are reported in homozygous mutants and the incidence of these patients in approximately 10 percent in Indian population. U.S. FDA has approved UGT1A1 testing before starting Irinotecan on a patient and have recommended “a reduced initial dose” to patients carrying UGT1A1*28 mutation.

Fluorouracil (DPD, MTHFR, TS)

5-FU (5-fluorouracil) has been a valuable drug against cancer. Dihydropyrimidine dehydrogenase (DPD), Thymidylate synthase (TS) and Methylenetetrahydrofolate reductase (MTHFR) are responsible for efficacy and toxicity from 5-FU. Hence, you can identify patients who will show severe toxicity to 5-FU. This is also mentioned in medical text books, international literature, and package insert of Xeloda. We are testing for the most common mutations in all these genes.

Methotrexate (MTHFR)

Methotrexate is a drug commonly used in treatment of leukemia and solid tumors. Methotrexate is an antimitobile drug and an analogue of folate. It interferes with folate metabolism by inhibiting dihydrofolate reductase, which leads to depletion of cellular folate. MTHFR is an important enzyme in maintaining cellular folate pools, and MTHFR gene variants associated with reduced enzyme function and hyperhomocysteinemia affect methotrexate sensitivity and contribute to toxicity. Commonly reported mutations in MTHFR gene are C677T and A1298C. These mutations cause reduction in enzyme activity. Patients having these mutations in MTHFR gene show severe side effects in cardiovascular, neurological, dermatologic, hematologic, hepatic, and gastrointestinal systems. These patients should receive a reduced dose based on their genotype.

References


4. “Drugs Don’t Work” by Dr Allen Roses, Worldwide Vice President of Genetics at GlaxoSmithKline

5. U.S. FDA Guidance for Industry, Pharmacogenic Data Submissions

Collection Centers

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