Acetylator Phenotype in drug metabolism Relevant to Pharmacogenomics and Pharmacogenetics: - an Overview

Charuvind K. Awale*, Rahul Mayee
1 SRM Clinical Research Services, Aurangabad, India.
corresponding author: charugenesis24@gmail.com
Received: 18/10/2011, Revised: 02/11/2011, Accepted: 12/12/2011

ABSTRACT
New era has arrived in the biological sciences and pharmaceutical sciences. The concept of personalize medicine used by health care organizations now days. This happens because the vast knowledge of genomics and genetics available now days but still much work is going to persist. Hence the terminologies as Pharmacogenomics or Pharmacogenetics uses very frequently due to great potential in both life sciences as well as pharmaceutical sciences research. In this, physicians or doctors would test each patient before treatment to prevent from lack of efficacy and avoid adverse drug reactions. This development is happens due to more knowledge of genetic components and proteomics to recognize the therapeutic medicine practice. This development is occurring due to correct metabolism of the routinely prescribed drugs.

KEYWORDS: Pharmacogenomics and Pharmacogenetics, Phenotypes, Acetylators, Acetylation Polymorphism.

INTRODUCTION
Today science has gone beyond the orthodox concept treating disease or disorder in human being. In next 10 to 20 years the term known as personalized medicine become more popular than traditional therapeutic medicine practice. This development is happens due to more knowledge of genetic components of individuals combination with Pharmaceutical science. Hence, awareness of important characteristic of individual increase because of genomic science. Hence research of drugs and treatment going to more focus on single individual in future which is not far away.

Pharmacogenomics and Pharmacogenetics
As per the normal designation of the Pharmacogenomics explain as it is science to study knowledge of genomics and proteomics to recognize the new drug targets and mechanism of their action. Whereas the Pharmacogenetics explains as it is science of to study the inter-individual specific genetic variation correlated to drug response. When these two ways comes together then it help to pharmaceutical and health care related sectors by facilitated by drug development and personalized medicine for more drug safety and prevents its adverse effects. But current scenario, the very few applications have shown successful outputs in clinical drug practices.

Personalized Medicine
This term defines its self that every individual get medical treatment according his or her genetic make-up. The two areas that notably signify patient’s safety concern are therapeutic failure & adverse drug events (ADEs). ADEs consist of both compliance issues & medical dispensing errors whereas Therapeutic failure refers to lack of efficacy because low quantity dose of medicine. Another main area as, adverse drug reactions (ADRs) are the side effects that occur even though appropriate administration of the correct medication at the ‘intended dose’. The ADEs are caused when there is occurrence of overload drug in the body for longer duration of time. The drug result is typically based upon the genetic make-up of an individual which is expected to demonstrate inter-individual variation in ‘genetic polymorphism’ in population. Hence, the intended dose might not prove suitable for every individual.

Phenotype
Phenotyping is one of the most general methods used to study genetic polymorphism to measure adverse drug effect. Phenotype is defined as the measurement of defined biochemical parameter or function. It requires ingestion of a probe drug; the metabolism of which is known to be exclusively dependent on one of the acylator enzymes such as N-acetyltransferase. It most common used to determine the presence and activity of a particular metabolizing enzyme in tissue biopsy. Phenotyping can be straightforward and invasive and potentially dangerous. Thus Phenotyping study separates the population of subjects in three main different types according to their genetic polymorphism into poor, extensive or ultra extensive metabolizers so that it can be used in standardizing the drug level in treatment for each individual.

Acetylation Polymorphism
In Pharmacogenetics the human Acetylation polymorphism is most important studied which motivate inter-individual and inter-ethnic differences in reply to xenobiotics. Genetic Polymorphism is defined as the inheritance of a trait controlled by a single genetic locus with two alleles , in which the least common allele has a frequency of about 1% or greater.
determined differences in N-Acetylation ability have proven to be important determinants of both the effectiveness of particular drug and the mode of adverse drug reactions and toxicity during medicinal treatment. Furthermore, many association studies have linked the Acetylation phenotype to vulnerability to a variety of complex human diseases as regarding asthma, cancer and other allergic disorders. There are two main genes are responsible for Acetylation Polymorphism as known as ‘Fast’ Acetylator and ‘Slow’ Acetylator. Here fast gene is dominant over slow gene. Each gene contains two alleles. Fast gene contains both fast alleles or one fast and other slow alleles whereas a slow gene contains both slow alleles. If individual contains fast gene then Acetylation polymorphism do not produce any adverse effect for drug. Slow gene creates complications in human due to poor metabolism in Acetylation polymorphism.

CURRENT STATUS OF METHODS FOR SCREENING OF ACETYLATION PROCESS OR ACETYLATOR PHENOTYPE

Acetylation is a phase II conjugation reaction occurring in human body that metabolises sulfamethazine, hydralazine, dapsone, isoniazid, aminoglutethimide, aminofide, and other drugs. The rate at which an individual acetylates these compounds has been found to be genetically determined, and the trait is inherited in an autosomal dominant fashion by a single gene. There are methods used for determine the action of Acetylator Phenotype by using various drugs in latest time period as follows:-

A) By using Sulfamethazine

The analysis of sulfamethazine (SMZ) kinetics in human has open complexities including wide inter subject variability. This attempt was made to review the potential influence of changes in non metabolic parameters on the markers of Acetylation capacity normally used in clinical screening procedures to determine phenotype. For example, seven normal subjects were classified as slow (SA) or fast acetylators (FA) according to their metabolic rate constant in blood and urine samples of human volunteers. In result, the computer simulations interpretations indicate that all the usual Phenotyping procedures were susceptible to changes in absorption and urinary elimination rate constants. While these predictions require experimental confirmation, results show that this method may minimize errors in Phenotyping screening.

Another preliminary study conducted for observing the relationship between sulfamethazine disposition kinetics and acetylation phenotype was studied in man. Sulfamethazine pharmacokinetic parameters were determined after the administration of the drug as an oral suspension. The failure to identify the assumed homozygous rapid acetylator using the commonly working indices of drug metabolism, i.e., half-life, metabolic rate constant, or per cent of the dose metabolized, was credited to a significant increase in the apparent volume of distribution of this genotype, as well as the low renal clearance of sulfamethazine found in all genotypes. This preliminary study points out the value of using metabolic clearance as an index of drug metabolizing capacity and suggests its application to further pharmacogenetic studies.

B) By using aminoglutethimide

Aminoglutethimide (AG) 500 mg was administered orally to four normal volunteers and eight patients undergoing treatment for metastatic breast cancer. Acetyl-aminoglutethimide (acetylIAG) rapidly appeared in the plasma and its disposition paralleled that of aminoglutethimide. In result of this experiment explains auto-induction of oxidative enzymes involved in aminoglutethimide metabolism.

C) By using Aminofide Dosing

Aminofide is extensively metabolized, including N-Acetylation to an active metabolite. Prior studies have demonstrated that patients who are fast acetylators of aminofide (and other drugs) have increased toxicity at standard doses of aminofide. The primary objective of this study was to define the recommended phase II dose of aminofide separately for slow and fast acetylators. Twenty-six patients with advanced cancer underwent acetylator typing with caffeine and were assigned to a dose level. Two patients were not typeable, and two patients appear to have been mis-phenotyped, one in each phenotype category. Pharmacodynamic analysis yielded a model for nadir WBC including acetylators phenotype, 24-h N-acetyl-aminofide plasma concentration, gender, and pretreatment WBC. They recommend doses of 250 and 375 mg/m2 (for 5 days) for further phase II testing of aminofide in fast and slow acetylators, respectively.

D) By Using Isoniazid

Isoniazid is still a widely used substrate to determine acetylator status, although dapsone is becoming increasingly popular as an alternative. Isoniazid would be preferred in patients with glucose-6-phosphate dehydrogenase deficiency to avoid haemolysis or in those already receiving isoniazid (which interferes with dapsone elimination). Also isoniazid may more clearly distinguish slow from fast acetylators have found dapsone to be unable to accurately phenotype subjects in 2-6% of cases. Although the half-life method is generally used to phenotype the human subject yet it has the disadvantages of being dependent on volume of distribution (Vd) which may vary in different cases and is inversely related to clearance and therefore product of metabolites. Since in fast acetylators, isoniazid undergoes extensive presystemic elimination, half life method would be relatively insensitive towards measuring the acetylation rate.

E) By Using Dapsone

Different methods have been reported for acetylator phenotype determination using isoniazid, sulphonamides and procainamide, but these have the disadvantages of multiple sampling, difficult analytical techniques or instability of the compounds measured. In 1971, Gelber et al. determined the ratio of monoacetyldapsone (MADDS) and dapsone (DDS) in plasma following a single dose of DDS and demonstrated that individual Acetylation characteristics for dapsone, isoniazid and sulfamethazine were the same. A specific, rapid and sensitive h.p.l.c. method for the determination of DDS, MADDS suitable for rapid allocation of acetylator phenotype in population studies is presented.
F] By Using Hydralazine

It is a drug of major importance in the treatment of hypertension. When used in combination with a diuretic and beta blocker, it has been shown to be effective in patients resistant to prior therapy. [30] It would be clinically useful to have a systematic method by which patient responsiveness to hydralazine might be predicted and dosing regimens optimized for individual patients. However, examples of inadequate blood pressure (BP) responses to regimens that include hydralazine are not infrequent. [31][32] The results of this experiment establish a relationship between plasma concentration of hydralazine as determined by a specific assay and the magnitude of hypotensive effect after oral administration of hydralazine. This correlation was significant following both single dose and the fifth dose of a series administered at 12-hour intervals. The experimental analysis implies that a major factor accounting for inter-individual differences in the response to oral hydralazine is the plasma concentration of the unmetabolized drug. Other factors, in particular the absolute level of pretreatment BP, may also be expected to influence the magnitude of response. [33]

CONCLUSION

The main purpose of this review is to focus on the importance of Acetylator Phenotype in drug metabolism and its application in various clinical laboratory practices by clinical practitioner. In current scenario of research recent interest in the influence of inherited patterns for the metabolism of foreign compounds in relation to drug toxicity and predisposition to disease has necessitated the importance of Acetylator Phenotype in drug metabolism and its application in various clinical laboratory practices by clinical practitioner. In current scenario of research recent interest in the influence of inherited patterns for the metabolism of foreign compounds in relation to drug toxicity and predisposition to disease has necessitated the

REFERENCES

21. A K Azad Khan, M Nurazzaman, and S C Truelove The effect of the acetylator phenotype on the