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PHARMENZYMONETICS AND PHARMGEONETICS: A NEW DOOR IN PHARMACOLOGY

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ABSTRACT

To introduce a new vision with an enhanced focus on the major factors contributing to pharmacokinetics and pharmacodynamics outputs at the level of both new drug introduction and clinical use of already appreciated medicines. Effect of enzymes, environment and genetic makeup on the pharmacology is discussed with a review of past focus by the scientists on such factors. The two terms are used for the first time solving the utmost problem in achieving therapeutic results by the scientists and patients. The meaning of two terms used in previous researches is illustrated briefly. People living in different countries experience different kinetic concentrations of medicines than literature value due to environment changes, enzyme variability and genetic transformations. Cmax, half-life, Vd, renal clearance and urinary excretion studies depicted marked variation due to change of enzyme and environmental factors among the individual of various origins and even among various individuals of same origin. For that two terms are coined pharmenzymonetics and pharmgeonetics. Advanced effects of medicine are entertained, enlightening cutting edge focus on the enzyme, environment and genetics prior study and treatment with a medicine to gain ideal or near to ideal therapeutic output.

KEYWORDS: Pharmenzymonetics, Pharmgeonetics, Pharmacology, Medicine Effect, Epigenetics.

INTRODUCTION

Advanced therapies including chemotherapy, vaccination and other drug intake do not get 100% therapeutic outcome in various individuals and even same species. Leaving behind the specie difference if we only see the human individuals there is a considerable difference in drug outcomes. When studied deeply the main factors which are notable include enzyme concentration changes due to change of environment and similarly genetic makeup which entertains the release of enzymes. Concentration change of enzyme puts fine change in the metabolism leading to change of whole therapeutic calendar of a medicine. A medicine approved for use in USA may not be used in Pakistan, Japan or Saudi Arabia with given dose and literature values. However serious eye on the pharmacological effect a medicine endorses needs to be kept where health condition of a whole country suffers. This is necessary to make kinetic and dynamic researches on the individual of those countries when only use of foreign manufacturer's medicine is an option. In this paper the two terms are elaborated using tamoxifen antiestrogen drug as key model for proving the new coined terms however, other drugs are also mentioned where necessary.

Pharmenzymonetics

" Pharmenzymonetics is the study of changed behavior of medicine in the living body due to enzyme and genetic makeup."

This term is thought to be responsible because multiple causes have been known to be involved in the metastatic breast cancer, but still chemotherapy is a question to absolutely treat this cancer (Shahbaz *et al.*, 2014) and possibly this question arises because of genotypical and phenotypical change of metabolic enzymes in the body. An enzyme Debrisoquine hydroxylase (CYP2D6) is known to affect the disposition kinetics of a lot of clinical medicines where people of different region show variable capacity of CYP2D6 substrate metabolism (Masimirembwa *et al*., 1996). In other cases the active site of the CYP2D6 is changed due to active medicament (Bapiro *et al*., 2002) and shows a metabolic correlation with the drug in different individuals where this study was done in Saudi Arabian people proving changed amount of enzymes in different people of different genetic makeup (McLellan *et al.*, 1997). Similarly the CYP2D6 genotype is different in Japanese people and other African countries where one variant is at higher frequency as compared to the other variant (Nishida *et al.*, 2000, Wennerholm *et al.*, 2002). CY2D6 activity variation may be genetic or inhibited by other drug however, in breast cancer patients chemotherapeutic effect

of tamoxifen significantly decreased because being prodrug changed to its active metabolite after action of CYP2D6 (Siegelmann-Danieli *et al*., 2011) and also effects risperidone metabolism (Yagihashi *et al*., 2009).

Many drugs show low bioavailability and other responses due to changed behavior of CYP3A4 substrates (Galetin *et al*., 2007, Maekawa *et al*.,2010 and Wang *et al* .,2011). Other CYP3A4 inducing agents such as rifampin highly decrease the concentration of toremifene and tamoxifen in the body and dose adjustment is required (Kivistö *et al*., 1998). Similarly the activity of CYP3A4 is regulated genetically (Angiolillo *et al*., 2006), same is true for other enzymes of P450 family that are controlled genetically and suggestd individual treatment plan (Ingelman-Sundberg., 2005) and CYP2C19 has shown to effect both pharmacokinetic and pharmacodynamic activites of certain drugs (Varenhorst *et al*.,2009).

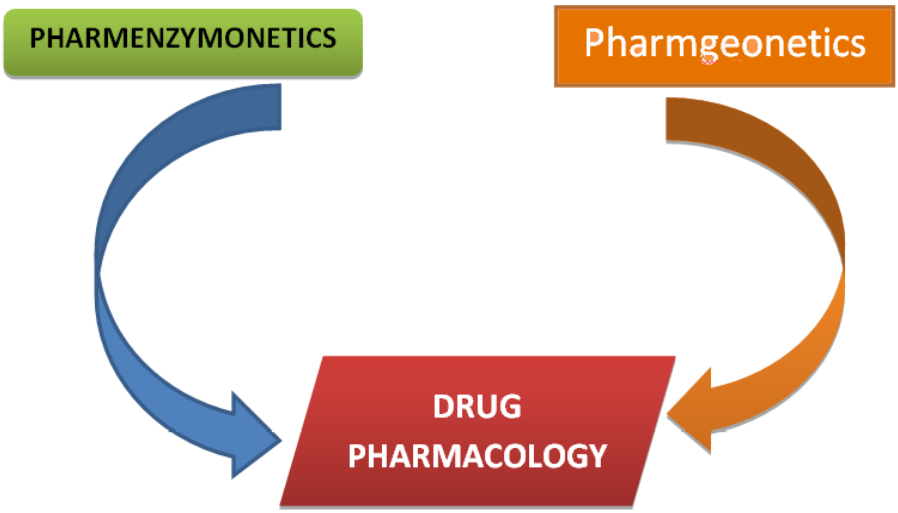

Fig 1. Diagramatic Illustration Of Effect Of Pharmenzymonetics And Pharmgeonetics On Drug Pharmacology.

Now it is clear the activity of enzyme changes the pharmacokinetic parameters in the individuals and also metabolic enzymes like CYP2D6 are inherited as deficiency from parents to offspring (Bertilsson *et al.*, 2002). Highly notable is when polymorphic genotype of CYP2D6 produces highest amount of N-Desmethyl tamoxifen (active metabolite) i-e. 48.6±1.52pmol/20 min/pmol CYP (Boocock *et al*., 2002) while in other individuals this level is up to 40ng/mL which clarifies that the role of enzymes in the pharmacology is pivotal due to genetic variations.

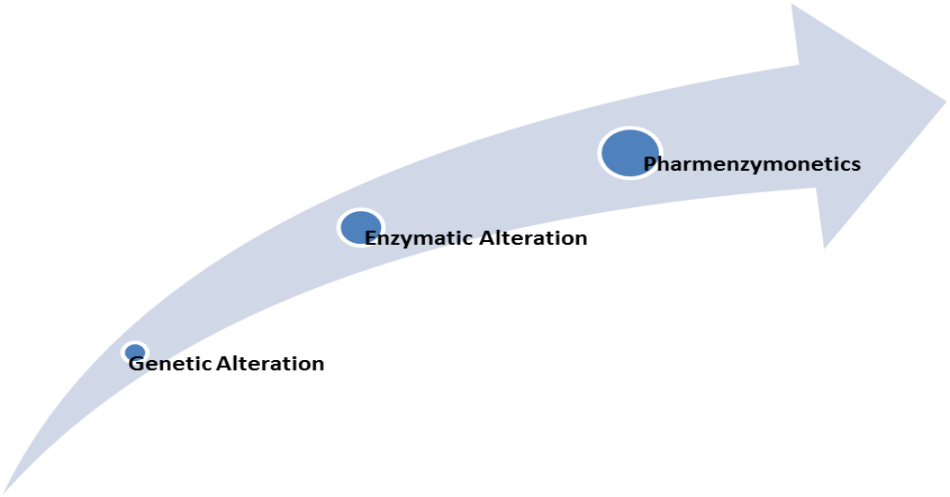

Fig. 2. Directional visualization that depicts change of genetics among people leads to changed enzyme level or existence ultimately proves pharmenzymonetics.

Few studies against Pharmenzymonetics

Older few research works where enzyme induction or enzyme inhibition do not catch any effect on the pharmacokinetics values like plasma clearance, half-life and Vd of the labetolol and on heart rate and diastolic blood pressure of the same drug after oral and IM administration (Daneshmend *et al*., 1984). Hence it was just inhibition or induction of enzyme with no reference of genetic outputs without which the term pharmenzymonetics is incomplete and also, above study is obsolete and blurred due to its age as ozone layer has changed a lot since then.

Pharmgeonetics

"Pharmgeonetics is the study of changed effect of medicine in the living body due to change of environment and genetic makeup."

This term is also used partially as geonetics (Nawaz *et al*., 2008) which elaborates the effect of environment and genetic factors, yet here it is explained as the study of changed effect of medicine due to environment and genetic factors. It is because epigenetic factors are also responsible here. Broadly the environment may change the genetic factors of some individuals and their attitude towards medicine will be changed. The environment effect is less on microevolution(genetic) than on the phenotypic (plastic components) which may lead us to epigenetic factors, yet the global warming and ethnicity of decades have selected particular traits (Gienapp *et al*., 2008) which shows a promising alteration to medicine response.

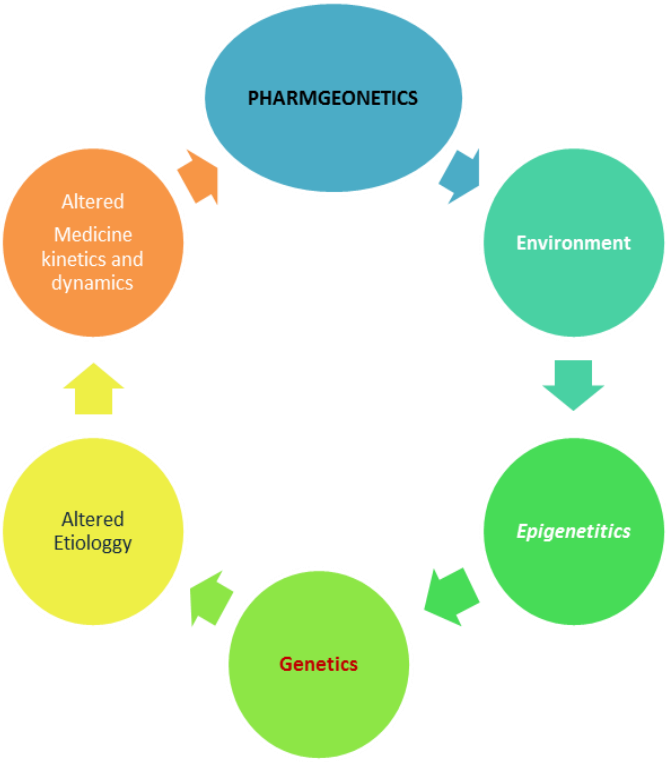

Fig. 3. Cyclic representation of pharmgeonetics describing how change of environment alters epigenetics, which through microevolution leads to genetics variation (Richards. 2006) and different etiology alters the pharmacology for particular medicine given in the same dose and direction as given in the literature.

The disposition kinetics of kanamycin in mules (Muhammad *et al*., 2003) and sulfamethoxazole excretion in cows (Baig *et al*., 1998) after single IV dose is widely changed from literature value in Pakistan as these drugs are imported from other countries. Similarly pharmacokinetics and pharmacodynamics studies are being done in the largest universities of developed and developing countries on many drugs in relation to humans and animals and even among the individuals of same species to get the therapeutic benefit.

Epigenetics are the key modulators pharmgeonetics providing evidences of changed drug response in various diseases both in animals and humans. The epigenetic studies is the key need of today to get the therapeutic outcomes of a drug or treatment. We are still working far away from the treatment standards and standard treatment guidelines.(Shahbaz *et al*., 2015) The tamoxifen has proved to be hepatocarcinogenic in rats and caused epigenetic factors thus it's a two way game where medicine is also effecting epigenetics (Tryndyak *et al*., 2006).

CONCLUSION

The Pharmenzymonetics and pharmgeonetics are blocking the real effects of medicine in a hidden way and demands extensive research and study at subject level. There are drugs which are enzyme dependent and those enzymes vary in their concentration at cellular and organ level among individuals. Similarly the environment is effecting our drug action both genetically and epigenetically. The next era is to focus on environment, enzymes, genetics, and epigenetics.

Recommendations

New world is now related to individual treatment plans where enzyme levels, environmental and genetic factors are kept under minute consideration of experts hence pharmacists and pharmacologist have a leading pivotal role and position. The drugs which are imported need to be used only after clinical trial has been done with in that country on children, adults and aged. The enzyme tests where enzymes are controlled genetically should be taken. Here the position of clinical pharmacist at the serious level is mandatory rather than on paper work level to maintain a better healthier world. This (individual treatment plan) concept is started in a small but bigger task company at Islamabad named Perfect Health Pvt Ltd.

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