WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 12, 507-514. Review Article ISSN 2277– 7105

PHARMACOGENOMICS IN EPILEPSY

Sruthi S. L.*[1], Sowparnika Treasa Sabu[2] and Prof. (Dr). Shaiju S. Dharan[3]

[1]Student, 5th Year PharmD, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Science.

[2]Assistant Professor, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Science.

[3]Principal, Ezhuthachan College of Pharmaceutical Sciences.

Article Received on
13 August 2020,

Revised on 03 Sept. 2020,
Accepted on 24 Sept. 2020,

DOI: 10.20959/wjpr202012-18817

***Corresponding Author**
Sruthi S. L.
Student, 5th Year PharmD, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Science.

ABSTRACT

Background: Due to lack of knowledge on pharmacogenomics & insufficient facilities available in this field many individuals are suffering from ADR, which result only due to genetic variation & the health care professionals are unable to alleviate the condition. By providing adequate knowledge & by introducing rapid testing procedures in this field it's possible to optimize the therapeutic efficacy. Pharmacogenomics pave way for precision medicine thus enable to minimize risk of ADR & also help the physician to identify contraindicated drug for a patient with a particular genetic variation. **Methods**: Previously published articles regarding the importance of pharmacogenomics in epilepsy have been collected and reviewed. **Observations**: It has been found that there is a great influence for pharmacogenomics in epileptic patients. Pharmacogenomic help to identify the defective gene thereby help the physician to adjust the dose as per their genetic variation this in turn help to minimize the risk of ADR. But still several improvements & contributions are needed to make this field an effective one.

KEYWORDS: Pharmacogenomics, AED, polymorphism.

INTRODUCTION

Epilepsy

Epilepsy can be defined as a chronic seizure disorder or group of disorder characterized by seizures that recur unpredictably in the absence of a consistent provoking factors. The main

symptoms include: temporary confusion, loss of awareness & psychic symptoms as fear, anxiety. Few antiepileptic drugs (AED) are: phenytoin, phenobarbitone, diazepam, clobazam, topiramate, gabapentin, valproate etc.[1] Mechanism of action of AEDs are:

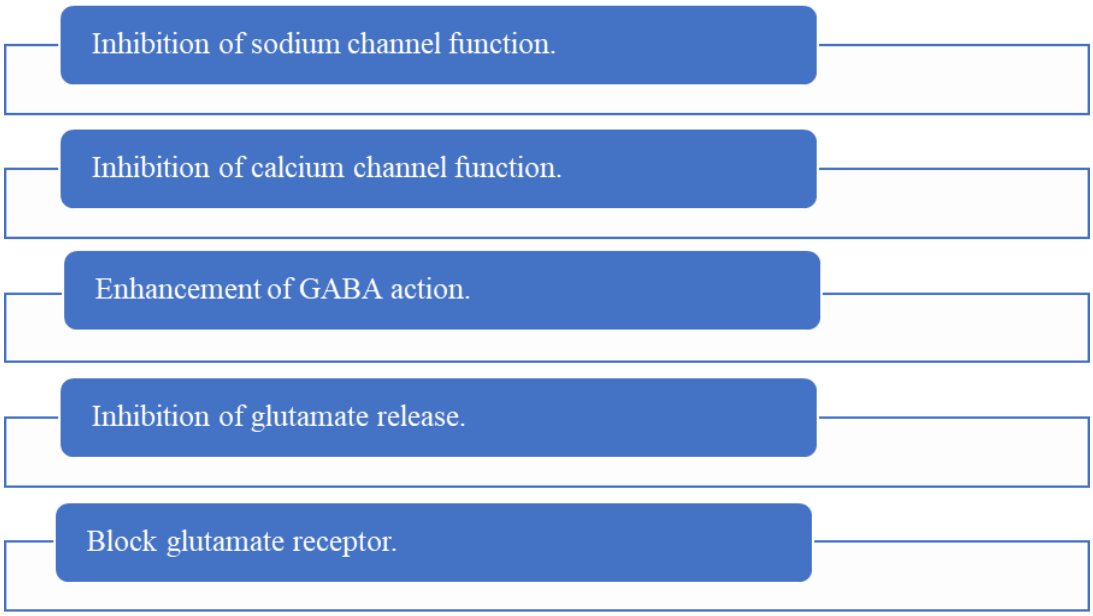

Figure 1: Mechanism of action of AEDs.

Epilepsy can also be treated by surgery as: resective surgery, laser intersititial thermal therapy, deep brain stimulation, corpus callosotomy, hemisphrectomy, functional hemisphrectomy.[2]

PHARMACOGENOMICS

Pharmacogenomics deals with influence of genetic variation on drug response by corelating gene expression or polymorphism with a drug's efficacy/ toxicity. It helps to identify who are prone/less likely to respond to drug and help to identify those who require altered dose of certain drug.[1] Gene mapping is method of determining the location of elements within a genome. Various methods of gene mapping include: genetic mapping(linkage mapping, pedigree, polymorphic marker), physical mapping(cytogenetic mapping, somatic cell mapping, radiation hybrid mapping, PFGE, BAC contigs),comparative mapping(gene sequence, data bases, DNA chips).GWAS (Genome Wide Association Study) is used for identifying genes responsible for disease & other trait.[2]

Importance of Pharmacogenomics In Epilepsy

Pharmacogenomics pave way for precision/ personalized medicine, is an approach to patient care that allow physician to select treatment based on genetic understanding of disease of

patient. For eg: advicing ketogenic diet to patient with mutation in gene coding for GLUT- 1 transporter. Response to AED & ADR experienced due to AED vary among population due to variation in phenotype & heterogenosity. Due to this variation pharmacokinetics (ADME) & pharmacodynamics(interaction with receptor, ion channels) will also vary thereby either increasing desired/ undesired effect of AED.[1] So by applying pharmacogenomics it will be possible to select best, safe, high efficacy AED as per individual patient condition & is also possible to reduce the risk of toxicity/ adverse events. Pharmacogenomics also help in identifying biomarkers of disease.[3]

A. Metabolising Enzymes & Adverse Events

AED are metabolized by CYP450 enzyme. CYP enzymes can be:

- Poor metabolizer: carry two defective allele.
- Intermediate metabolizer: carry 1 wild type & 1 defective allele.
- Normal metabolizer: carry wild type allele.
- Extensive metabolizer: carry one wild type & one amplified gene.
- Ultra rapid metabolizer : carry two/ more copies of amplified gene.[3]

Polymorphism in genes coding for this enzymes may alter metabolism of AED & in turn can lead to neurotoxicity, as mutated allele will produce enzyme which has less capacity to metabolize AED. So in such individual pharmacogenomics play a vital role in dose selection to protect them from the effects of neurotoxicity. Any gene that doesn't encode for AED target also cause variation in drug response.[4] Phenytoin is metabolized by CYP2C9 & to a little extent by CYP2C19.Polymorphism in genes coding for these may induce ADRs as dizziness, nystagmus, mental confusion. Drugs as carbamazepine, lamotrigine is metabolized by UGT enzyme. Polymorphism in gene coding for them will alter plasma concentration of above mentioned drugs & in turn lead to ADR as: liver damage, metabolic change, tremor, excessive weight gain. So for patient with polymorphism, dose of phenytoin, carbamazepine & lamotrigine should be adjusted to minimize toxicity risk. Polymorphism in ABCG2 gene alter lamotrigine disposition and lead to ADR.[5]

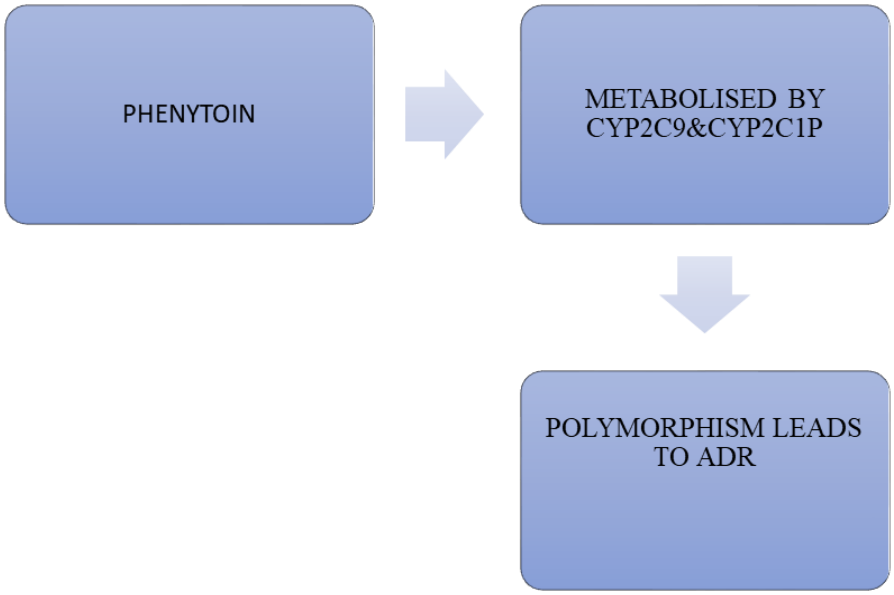

Figure 2: Metabolising Enzyme & Adr.

Cutaneous ADR to AEDs

These are of various types as: maculopapular eruption, urticaria, AGEP(acute generalized exanthematous pustulosis), vasculitis, DRESS(drug reaction with eosinophilia & systemic symptoms), DIHS (drug induced hypersensitivity syndrome), Stevens Johnson Syndrome(SJS), Toxic Epidermal Necrolysis(TEN)etc. These ADRs are either due to hapten – carrier complex formation or pharmacological interaction between drug & immune receptor. In the former, drug act as hapten & bind with protein molecule to form a complex which in turn activates T cell & stimulate clinical manifestations. In the latter mechanism, drug bind with immune receptor such as MHC to activate T cells & produce symptoms as SJS, TEN.[6]

B. Drug Transporter

Activation of voltage gated KCNQ potassium channel help to reduce risk of sudden unexpected death in epilepsy.[7] Individuals with autoimmune disorder also show altered plasma drug concentration as compared with controls. Some epileptic patient develop resistance to AED due to polymorphism of gene coding for P- gp transporter in brain tissues. Dravet syndrome is a genetic condition characterized by prolonged seizures & is caused by mutation in SCN1A gene. This gene codes for sodium channel. Sodium channel has 2 sub units α & β coded respectively by SCN2A & SCN3B gene. Mutation causing Dravet syndrome is inherited in an autosomal manner i,e. one faulty copy of disease causing gene is sufficient to develop this condition. Treatment option include: valproate, topiramate,

clobazam, stiripentol, ketogenic diet. But the choice of treatment depends on location, nature & type of gene mutation. Mutation in GR1N2 & KCNQ2 genes lead to epileptic encephalopathy. Treatment option for former is memantine, NMDA receptor antagonist & for latter is retigabine, it act on potassium channel & affect GABA neurotransmission in GABA A receptor which is a inhibitory receptor in CNS. Urea cycle disorder arise due to deficient in any urea cycle enzymes as arginase, arginosuccinate synthetase, arginosuccinate lyase, orinithine transporter etc.. resulting in hyperammonemia, encephalopathy, respiratory alkalosis. Valproic acid is contraindicated in such patients because of increased risk of hyperammonemia & encephalopathy. Alpers Huttenlocher syndrome, is a genetic mitochondrial disease caused by mutation of polymerase DNA directed gene on chromosome 15. This gene is responsible for DNA synthesis. Symptoms of this syndrome include: seizure, liver disease. Valproic acid is contraindicated in such patients due to increased risk of drug induced liver toxicity. Patient with mitochondrial disease have inborn error of fatty acid oxidation in mitochondria. So the knowledge of pharmacogenomics help to avoid ADR related to valproic acid in these patients. ABC transporter are transmembrane protein that utilizes the hydrolysis of ATP to facilitate movement of substrate across membrane double layer. ABC2 is transporter of ABC superfamily for which phenytoin, valproic acid, carbamazepine are substrate. Polymorphism in genes coding for these transporter cause ADR as: diplobia, somnolence, headache.

C. Dose Adjustment

By identifying inheritance difference in each individual it's possible to predict the response to treatment thereby help in dose adjustment.[8] By using genetic mapping, dose of many AED can be altered as per patient need. As compared to normal patient, patient with variation in gene coding for CYP2C9 & CYP3A4 require dose adjustment as these mutations alter normal serum concentration of drug & in turn lead to increased desired/ undesired effect. CYP2C9 & CYP3A4 respectively metabolizes phenytoin & carbamazepine. For individuals with extensive metabolizer no dose adjustment is needed but for those with intermediate & poor metabolizer 25% & 50% dose reduction is needed respectively to achieve desired therapeutic response/to decrease the risk of ADR. Epoxide hydrolase I is an enzyme that metabolizes compound with epoxide residue to a substrate with hydroxyl residue through dihydroxylation reaction, thus they are made more water soluble & can be eliminated easily. Epoxide hydrolase I is responsible for metabolizing carbamazepine. Due to mutation in gene coding for this enzyme, their metabolism is altered, therefore, dose reduction is needed as compared

to normal individuals. If this dose adjustment is not made it will lead to ADR, even cause teratogenic effects as craniofacial abnormalities. So, here comes the role of pharmacogenomics in identifying defective gene & in turn aid to reduce dose of AED thus minimizing risk of ADR. Thus, its clear that genetic variation will alter safety, efficacy & tolerability of AEDs.[9] Seizure susceptible gene can be identified either by identifying the therapeutic target or by identifying the patient subgroup that contribute to the genetic variation.[10] So pharmacogenomics aid to minimize ADR & maximize drug safety & efficacy.[11]

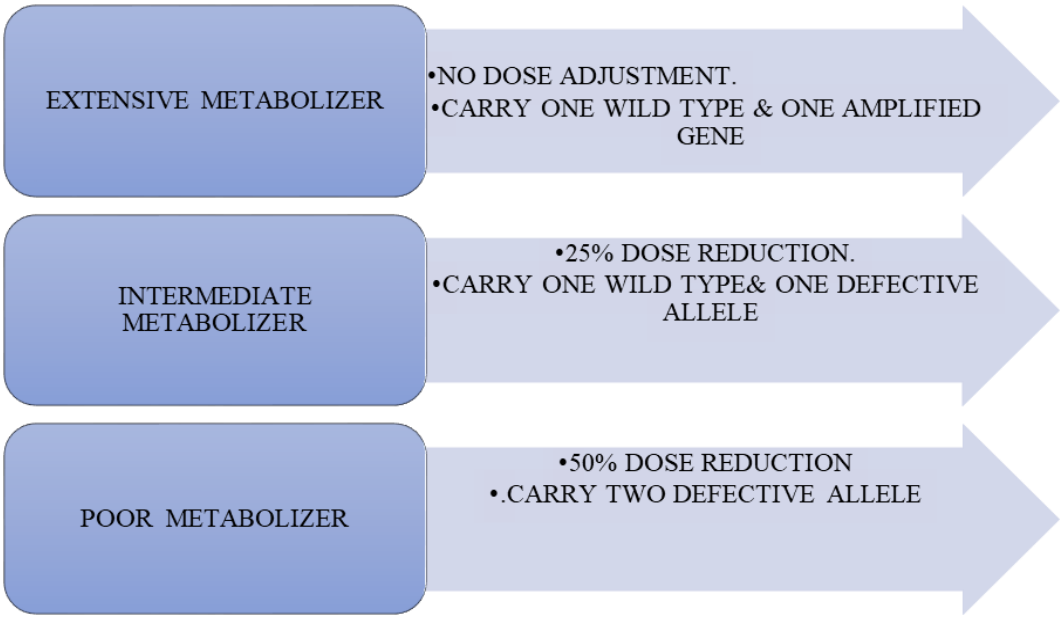

Figure 3: Type & Dose Adjustment In Different Cyp Enzymes.

Barriers of Pharmacogenomics

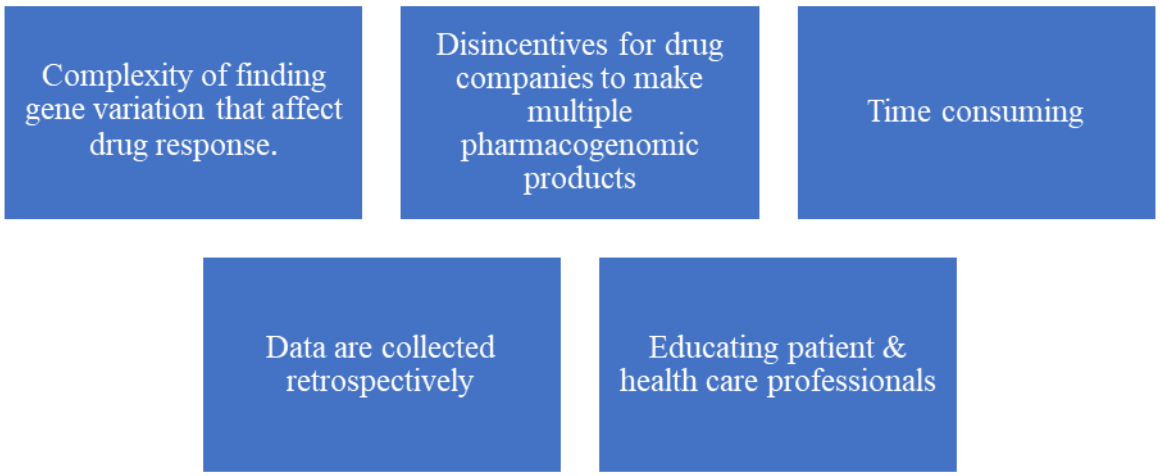

Figure 4: Barriers of pharmacogenomics(2).

CONCLUSION

From above mentioned examples it's clear how relevant is pharmacogenomics in treating a disease condition. This knowledge helps the physician to provide the patient the right drug at right dose to achieve the desired therapeutic outcome/to minimize the risk of ADR and thus protecting the patient from further complications. If we are able to overcome the obstacles as mentioned earlier in the field of pharmacogenomic, it would have such a profound effect on our healthcare system.

REFERENCES

1. Pharmacogenomics in epilepsy, Simona Balestrini, Sanjay M Sisodiya, neuroscience letters, 2018; 27-39.
2. Pharmacogenomics and epilepsy: the road ahead, Gianpiero L Cavalleri†, Mark McCormack, Saud Alhusaini, Elijah Chaila & Norman Delanty, research gate, 2011; 1429-1447.
3. Pharmacogenetics of antiepileptic drugs: A brief review, D. Parker, E. J. Sanders, K. J. Burghardt, Mental Health Clinian, 2016; 6(1): 28-34.
4. Effect of GRM4, SCN2A & SCN3B polymorphism on antiepileptic drugs responsiveness and epilepsy susceptibility, Laith N AL-Eitan etal, Saudi pharmaceutical journal, 2019; 731-737.
5. Interaction between ABCG2 421C>A polymorphism and valproate in their effects on steady-state disposition of lamotrigine in adults with epilepsy, British Journal of Clinical Pharmacology, 2018; 84: 2106–2119.
6. Pharmacogenetics of adverse reactions to antiepileptic drugs, Fricke-Galindoa, H. Jung Cookb, A. LLerenac, M. López-López, Neurologia, 2018; 33(3): 165-176.
7. Pharmacogenetics of KCNQ channel activation in two potassium channelopathy mouse models of epilepsy, Stephanie L. Vanhoof-Villalba, Nicole M. Gautier, Vikas Mishra, and Edward Glasscock, Department of Cellular Biology and Anatomy, Louisiana State University Health Sciences Center, 2019.
8. Roses AD. Pharmacogenetics and the practice of medicine. Nature, 2000; 405(6788): 857-65. DOI: 10.1038/35015728. PubMed PMID: 10866212.
9. Lo¨scher W, Klotz U, Zimprich F, Schmidt D. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia, 2009; 50(1): 1-23. DOI: 10.1111/j.1528-1167.2008.01716.x. PubMed PMID: 18627414.

10. Discovery of epilepsy susceptibility genes: implications for therapy development and pharmacogenomics, Thomas N Ferraro, Pharmacogenomics, 2012; 13(7): 731–734.
11. Klotz U. The role of pharmacogenetics in the metabolism of antiepileptic drugs: pharmacokinetic and therapeutic implications. Clin Pharmacokinet, 2007; 46(4): 271-9. DOI: 10.2165/ 00003088-200746040-00001. PubMed PMID: 17375979.