

## Phenytoin in Personalized Medicine

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Epilepsy is a long running; heterogeneous neurological disease which is characterized by recurrent seizures. Smoking, lack of sleep, non-compliance of drugs are the main precipitating factors of epilepsy[1]. Phenytoin (PHT), Carbamazepine (CBZ), Phenobarbital (PBT) and Valproic Acid (VPA) are primary antiepileptic drugs (AEDs) used in the treatment of epilepsy. Other than these primary AEDs, many new generation AEDs are also available in the market such as lamotrigine (LTG), levetiracetam (LVT), oxcarbazepine (OXC), topiramate (TPM), pregabalin (PGB), gabapentin (GBP), zonisamide (ZNS) etc [1]. Despite these new AEDs, PHT is extensively used in the treatment of partial and generalized epilepsy. PHT is also given in traumatic brain injury induced epileptogenesis which decreases the quality of life of the affected patients[3]. PHT has narrow therapeutic range (10 - 20 µg/ml), below the level of 10 µg/ml it follows zero order kinetics and above this level it follows first order kinetics and shows some adverse drug reactions [2]. Some patients show side effects and some patients show good response to the same drug at same dose because of personalized medicine. Adverse drug reactions (ADRs) associated with PHT are dose dependent and dose independent. Dose dependent ADRs are cerebellar ataxia, nystagmus, sedation, diplopia and in dose independent ADRs, the most common adverse drug reactions are hypersensitivity. Other than these ADRs, gingival overgrowth or gum hyperplasia is also included in both categories [3]. There is broad inter-individual variations in PHT metabolism which depends on patient's age, sex, genetic profile, ethnicity, hepatic, and renal functions. Thus, it is not possible to foretell whether a patient will experience PHT associated side effects or not. To overcome this problem, therapeutic drug monitoring (TDM) is recommended in the patients to avoid toxicity [4]. PHT is metabolized mainly by CYP2C9 (90%) and to a lesser extent by CYP2C19 (10%). Genetic polymorphisms of these genes are associated with ADRs by decreasing metabolism therefore, increasing the concentration of PHT in the blood. Mainly alleles 2 and 3 of genes CYP2C9 and CYP2C19 are involved in the toxicity of PHT and allele 2 of gene CYP2C9 is involved in idiosyncratic drug reaction related with PHT in epilepsy [5]. Even HLA-B\*1502 is also present in these type of idiosyncratic drug reactions. Some studies showed that HLA-B\*1502 is present in CBZ induced-SJS-TEN (Stevens-Johnson Syndrome- Toxic Epidermal Necrolysis) patients but not PHT-induced, the worst form of idiosyncratic drug reactions in which almost 10 - 30% of the skin is removed due to ADRs. Some studies showed that PHT induced IDRs can be because of HLA-B\*1502 and HLA-A\*3101 [6]. So it is recommended that detection of these alleles and HLA typing should be done before starting PHT therapy in epilepsy.

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### Conflict of Interest

None.

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