Bahrain Medical Bulletin, Vol. 39, No. 1, March 2017

MDR1 Gene Polymorphism and Phenytoin Pharmacokinetics in Epilepsy

Adel Ali Alhazzani, MD* Murali Munisamy, PhD**
Gauthaman Karunakaran, PhD***

Background: Pharmacokinetics is a widely used anti-epileptic drug phenytoin, which exhibits noticeable inter-individual variations in efficacy. Genetic factors, such as MDR1 gene polymorphism may play a crucial role in drug response.

Objective: To investigate the influence of MDR1 variant genotypes on Phenytoin Pharmacokinetics in epileptic patients.

Design: A Case-Control Genetic Study.

Setting: College of Medicine and Pharmacy, King Khalid University, Abha, Saudi Arabia.

Method: Twenty-five epileptic patients non-responders to phenytoin monotherapy and 25 epileptic patients' responders to phenytoin monotherapy were recruited. DNA was isolated by conventional phenol-chloroform method. MDR1 (3435C>T) gene polymorphism was assessed using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphisms (PCR-RFLP) method. Allelic and genotypic frequency were calculated. Reversed-phase High-Performance Liquid Chromatography (HPLC) method was used to determine the plasma levels of Phenytoin drug. PK Solutions was used for non-compartmental analysis to estimate the pharmacokinetic parameters.

Result: The MDR1 (3435C>T) polymorphism was found to be in Hardy–Weinberg equilibrium and displayed significant allelic and genotypic association between non-responders and responders to phenytoin ($P<0.01$). The finding of pharmacokinetics analysis demonstrated that longer half-life ($t_{1/2}$ = 33.26 hours) and less clearance rate (CL = 0.42 L/hour) in the homozygous variant group compared to wild-type genotype group ($t_{1/2}$ = 19.2hrs, CL = 0.8 L/hour).

Conclusion: The finding suggests that the genetic polymorphism in the C3435T location of MDR1 gene might determine pharmacokinetics variability of phenytoin drug. Therefore, pharmacokinetics parameters along with genotyping of MDR1 (C3435T) genotype might be valuable in the perspective of personalized medicine in epileptic patients.

---

* Assistant Professor of Neurology
Department of Neurology, College of Medicine
** Assistant Professor
Department of Pharmaceutics, College of Pharmacy
*** Associate Professor
Department of Pharmacology, College of Pharmacy
King Khalid University, Abha
Kingdom of Saudi Arabia
E-mail: alhazzani@kku.edu.sa, aalhazzani@yahoo.ca