Personalized Medicine
Phenytoin Therapy

INTRODUCTION
Phenytoin is one of the anti-seizure drugs most widely prescribed. This drug has narrow therapeutic index. This drug was indicated on tonic clonic seizures (general convulsions), partial seizures, seizures during neurosurgery and seizure due to head trauma. Because of narrow therapeutic index and the use of often long-term, therapeutic drugs monitoring (TDM) is necessary.

Molecular formula and structure of phenytoin
Phenytoin (C$_{15}$H$_{12}$N$_{2}$O$_{2}$) has molecular weight: 252.268 da. The structure of this medicine is given in Fig. 1.

Mechanism of action
Phenytoin changes the conductance of Na$^{+}$, K$^{+}$ and Ca$^{2+}$, membrane potential and the concentration of amino acids and neurotransmitters, norepinephrine, acetylcholine and GABA (gamma amino butyric acid). These drugs also inhibit post-tetanic potentiation in the spinal cord. In high concentrations, these drugs inhibit the release of serotonin, norepinephrine, and increase dopamine uptake and inhibit the action of monoamine oxidase.

Pharmacokinetic profile
The absorption rate of phenytoin varies from 1 to 12 hours, with a bioavailability >80%. The protein binding of phenytoin was about 90%. Phenytoin rapidly was metabolized by CYP2C9 (major) and CYP2C19 (minor) into two forms of metabolite namely 5- (p-hydroxyphenyl) -5-phenylhydantoin and dihydrodiol derivative. The half of life ($t_{1/2}$) of this drug varies in individual (30–100 hours). There is a wide variation between individual dose related and phenytoin concentration in the serum. The serum levels of phenytoin within a range of 10–20 mg/mL (40–79 μmol/L).

Metabolism of phenytoin
The metabolism of phenytoin is due to hydroxylation by Cytochrome p450 (CYP). This metabolism was catalyzed by CYP2C9 and CYP2C19.
Polymorphism of CYP2C9 and CYP2C19 and pharmacologic effect

CYP2C9 is a major enzyme in the liver that catalyzes several drugs including phenytoin. Some of the genetic variations (polymorphisms) in genes forming this enzyme have been mapped. CYP2C9*1 is wild type while CYP2C9*2 and CYP2C9*3 are variant type. There is a substitution of cytosine by arginine (Arg144/Cys) in CYP2C9*2, while substitution of leucine by isoleucine (Ile359/Leu) in CYP2C9*3 and the substitution of cytosine by tyrosin on base 358 (Tyr358/Cys). This impacts the enzyme ability to catalyze a substrate metabolism.

Research on epilepsy patients in Korea (n = 97) concluded that patients with mutant type of CYP2C9 and CYP2C19 have plasma phenytoin higher than wild type. The epilepsy patients with mutant alleles of CYP2C9 require a lower dose to reach therapeutic levels compared with wild type (199 mg/day versus 314 mg/day; P < 0.01).

The CYP2C19 polymorphism is caused by a point mutation in exon 4 (G→A) (CYP2C19*2) and G→A in exon 5 (CYP2C19*3). The polymorphism of CYP2C19*2/2, *3/3, or *2/*3 causes functional defects of this enzyme and a decrease in the drug metabolism catalyzed by this enzyme. There are elevated levels of phenytoin in homozygous CYP2C9*2 allele, heterozygous CYP2C19*4 allele and homozygote of the ABCB1 3435C and 12364C alleles after the infusion of phenytoin.

Research by Veronese et al., found that there are elevation of phenytoin hydroxylation in individuals with Ile359→Leu. Research conducted in Japanese subjects with the type of CYP2C9 and CYP2C19 showed that there are differences in the variant of the concentration of steady state (Css). Individual groups of wild-type (CYP2C9*1/*1 and CYP2C19*1/*1) have phenytoin Css 6.6 ± 4.8 μg/mL at doses of 3.58 ± 1.48 mg/day/μg (Css/dose = 1.7 ± 0.8), while individuals with the variant type (CYP2C9*1/*1 and CYP2C19*1/*2 and *3) have phenytoin Css 8.1 ± 5.6 μg/mL at dose of 2.95 ± 1.36 mg/day/kg (Css/dose = 2.2 ± 0.9). Individuals with CYP2C9*1/*3 and CYP2C19*1/*1;*1/*2 and *1/*3 have Css 4.7 ± 20 pg/mL at dose of 2.09 ± 0.17 mg/day/μg (Css/dose = 2.2 ± 0.8).

The treatment of phenytoin and acenocoumarol simultaneously in individuals with CYP2C9*3 increases the risk of phenytoin acute toxicity. This occurs due to decreased metabolism of both drugs. The treatment of phenytoin in Thai with HLA-B*1502 allele increases the risk of Steven Johnson syndrome. A study involving 100 people with epilepsy in Egypt showed that there are significant difference of plasma phenytoin caused by adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) polymorphism. A total of 13 subjects with ABCB1 TT gene had very higher plasma phenytoin than CC type. Epileptic patients with homozygous CYP2C9*6 which occurs adenine deletion in 818 bp, have phenytoin clearance lower than in control subjects (approximately 17%).

Research conducted in Bugis ethnic in Indonesia found that the frequency of CYP2C19*3 and CYP2C19*17 allele were 1.56% and 4.68%, respectively.

CONCLUSION

The polymorphism CYP2C9 and CYP2C19 gene influence pharmacokinetic and pharmacodynamic of phenytoin. Therapeutic drug monitoring (TDM) is required to phenytoin treatment specially on people with variant type of CYP2C9 and CYP2C19.

REFERENCES


