Article Review

Association between CYP2C9 and CYP2C19 Polymorphism, Metabolism, and Neurotoxicity after Administration of Phenytoin: A Systematic Review

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Abstract—*Phenytoin is an antiepileptic drug (AED) metabolized by cytochrome P450 enzymes, especially by CYP2C9 (90%) and CYP2C19 (10%), where both enzymes are polymorphic so that they can undergo polymorphism and it can change the metabolic rate of the drug. Phenytoin is one of the drugs whose risk of side effects may increase due to its narrow therapeutic window of 10-20 µg/mL if the metabolism is slow.* ***The main literature was taken from publications through the library databases in 2017 – 2021.*** *Studies and reviews describing the metabolism, CYP2C9 and CYP2C19 polymorphisms, and neurotoxicity of phenytoin were included, and unrelated research were excluded.* ***There were 18 of 853 articles*** *describing CYP2C9 and CYP2C19 polymorphisms, metabolism, and neurotoxicity events associated with phenytoin used. The authors conclude that based on the results from various literature, there is an association between CYP2C9 and CYP2C19 polymorphism, metabolism, and neurotoxicity after Phenytoin administration with CYP2C9*2 and CYP2C9*3 types of polymorphisms for CYP2C9 and CYP2C19*2 and CYP2C19*3 types for CYP2C19*3 enzymes which can slow down the phenytoin metabolism and increase its concentration in serum so that the risk of causing neurotoxicity.*

Keywords: *CYP2C9, CYP2C19,metabolism, neurotoxicity, phenytoin*

Abstrak—Fenitoin merupakan obat antibangkitan yang dimetabolisme oleh enzim sitokrom P450 terutama oleh CYP2C9 (90%) dan CYP2C19 (10%), dimana kedua enzim tersebut bersifat polimorfik sehingga dapat mengalami polimorfisme dan dapat mempengaruhi laju metabolisme obat. fenitoin merupakan salah satu obat yang risiko efek sampingnya dapat meningkat jika metabolismenya lambat karena jendela terapeutiknya yang sempit, yaitu 10-20 µg/mL. **Literatur utama diambil dari publikasi melalui database perpustakaan tahun 2017 – 2021**. Penelitian dan ulasan yang menggambarkan metabolisme, polimorfisme CYP2C9 dan CYP2C19, dan neurotoksisitas fenitoin, dan penelitian yang tidak terkait dikeluarkan. **Terdapat 18 dari 853 artikel** yang menjelaskan polimorfisme CYP2C9 dan CYP2C19, metabolisme, dan kejadian neurotoksisitas terkait dengan fenitoin yang digunakan. Peneliti menyimpulkan bahwa berdasarkan hasil dari berbagai literatur, terdapat hubungan antara polimorfisme, metabolisme, dan neurotoksisitas CYP2C9 dan CYP2C19 setelah pemberian fenitin dengan jenis polimorfisme CYP2C9*2 dan CYP2C9*3 untuk CYP2C9 dan CYP2C19*2 dan CYP2C19*3 jenis enzim CYP2C19*3 yang dapat memperlambat metabolisme fenitoin dan meningkatkan konsentrasinya dalam serum sehingga berisiko menyebabkan neurotoksisitas.

Kata kunci: *CYP2C9, CYP2C19, fenitoin, metabolisme, neurotoksisitas*

INTRODUCTION

Phenytoin is an antiepileptic drug that has been used extensively for eight decades in controlling focal seizures and status epilepticus and has been clinically evaluated [1,2]. Phenytoin has a voltage-gated mechanism that stabilizes the inactive state of Na+ channels (sodium channel blockers) and extends the refractory period of nerves related to the release of neurons with abnormally high frequencies but no impact on normal frequencies [1]. In addition, Phenytoin also influences postsynaptic responses and the transmission of several Ca^{2+}-dependent neurotransmitters [1].

The metabolism of phenytoin is complex, with its elimination via several biotransformation pathways. Phenytoin is converted to (R,S)-5-(p-hydroxyphenyl)-5-phenyl-hydantoin (p-HPPH) and dihydrodiol which can undergo the formation of reactive arena oxide intermediates which can play a role in several actions of expenditure in the body such as pathogenicity, hepatotoxicity, serious skin reactions, and teratogenicity. Besides being able to form these intermediates, p-HPPH will be further metabolized into glucuronide and catechol

derivatives [2,3]. Cytochrome P450 is an enzyme that metabolizes phenytoin, especially the CYP2C9 and CYP2C19 enzymes [2,3].

Polymorphisms are events that can occur in genes encoding drug transport proteins, drug receptors, and drug-metabolizing enzymes, which can affect drug disposition, cause side effects and may require dose adjustment of the drug to the polymorphism [4]. CYP enzymes are enzymes that can undergo genetic polymorphisms so that they can reduce the metabolism of phenytoin which results in the high availability of the drug in the body [5]. The main enzyme in phenytoin metabolism that is responsible for 90% of the conversion of phenytoin to p-HPPH (the main metabolite) is CYP2C9 and the remaining 10% is the responsibility of CYP2C19. Therefore, polymorphisms in these two enzymes can result in the disruption of phenytoin metabolism, especially in CYP2C9 which will result in a 25-50% decrease in phenytoin metabolism compared to patients with normal metabolism [2].

Phenytoin is one of the drugs that have a narrow therapeutic window, which is between 10-20 µg/mL, where generally 90% of phenytoin is bound to plasma proteins and unbound which is physiologically active so that patients with decreased plasma binding of phenytoin will show signs of toxicity at normal doses [6]. Plasma concentrations of less than 10 µg/mL will cause a less than optimal therapeutic effect, whereas if plasma concentrations exceeding 20 µg/µmL can increase toxicity. CYP2C9 and CYP2C19 which undergo genetic polymorphisms can result in a decrease in phenytoin metabolism which can cause toxicity due to an increase in plasma drug concentrations [7]. Excessive levels of phenytoin can induce peripheral neuropathy and cause celestial dysfunction and inhibit the central nervous system. In addition, pseudolymphoma and malignant lymphoma, gingival hyperplasia, and allergic reactions may occur due to excessive phenytoin levels [2].

There is a large body of literature describing the incidence of neurotoxicity such as dizziness, tremor, dysarthria, nystagmus, ataxia, comma, and death. following phenytoin administration. However, no studies are showing a correlation between CYP2C19 and CYP2C9 polymorphisms, metabolism, and the incidence of neurotoxicity after phenytoin administration in one article. Therefore, we write down the relationship between some of these things and summarize them in this research.

MATERIALS AND METHOD

Study Protocol

This study will examine the relationship of related variables obtained from the database using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement guide [8]. Databases we have used from Science Direct, Medline/PubMed, Nature, SpringerLink, and Google Scholar. The type of literature sought is literature from the database for the last five years (2017 – 2021) in the form of research articles and reviews. Studies that may comply with inclusion criteria are published based on the title of the study and relevant abstracts according to guidelines from PRISMA.

Inclusion and Exclusion Criteria

The inclusion criteria were: (1) Studies published in the last 5 years in the form of experiments, reviews, case reports, and cross-sectional studies, (2) Reviews and studies explaining metabolism, CYP2C9 polymorphisms, and CYP2C19, phenytoin neurotoxicity. While the exclusion criteria for this review article were: (1) Duplication of studies, (2) Cohort studies, (3) Opinion studies, (4) Studies written in languages other than English and Indonesian, and (5) Studies not related to the study.

Search Study

We searched the literature using international databases from Science Direct, Medline/PubMed, Nature, SpringerLink, and Google Scholar search engine with the keywords

"Phenytoin", "CYP2C9", "CYP2C19", "polymorphism", "metabolism", and "neurotoxicity" from the last five years to 2021.

Selection of Studies

All search results obtained from the collected literature were filtered and all duplicates from the search results were removed. Screened studies are assessed based on inclusion and exclusion criteria through titles and abstracts from related studies, but if the assessment based on titles and abstracts alone is doubtful, then it can be assessed based on the full text of the article.

Data Collection

We compiled studies based on the characteristics of the year of publication, title, author, methods, and study design including adverse effects on neurotoxicity and other brain disorders. Data following the inclusion and exclusion criteria are reviewed and a conclusion is drawn.

Quality Assessment

All selected sources were evaluated for quality using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) bias risk assessment tool template [9]. The risk assessment of bias studies was carried out independently using the Robvis App to create bias risk plots and graphs. The criteria for this assessment are four domains: year of publication, research topic, research design, and method of analysis. There are three answers, namely "yes", "no", or "unclear", where the risk of bias is low if the answer is "yes". While the risk assessment of bias can be assessed into three parts, namely "low", "high", or "some concern".

RESULTS

Study selection and results

Based on a predefined search method, 853 studies were found through databases and websites. Study duplication was found in 153 articles from search results, 183 articles did not meet the requirements and 212 articles were deleted for other reasons, leaving 305 articles. Then, after being assessed based on the title and abstract, 110 articles were excluded because they did not meet the criteria. 38 of the remaining 195 articles were excluded due to data discrepancies with the study. Of the remaining 157 articles, 127 articles did not meet the inclusion criteria with 5 of them using languages other than Indonesian and English so they were excluded from the study. Of the 30 eligible articles, there were **18** articles describing CYP2C9 and CYP2C19 polymorphisms, metabolism, and neurotoxicity events associated with phenytoin used. The results obtained from the study did not contain quantitative data so we did not carry out statistical or meta-analysis. This process is shown in Figure 1.

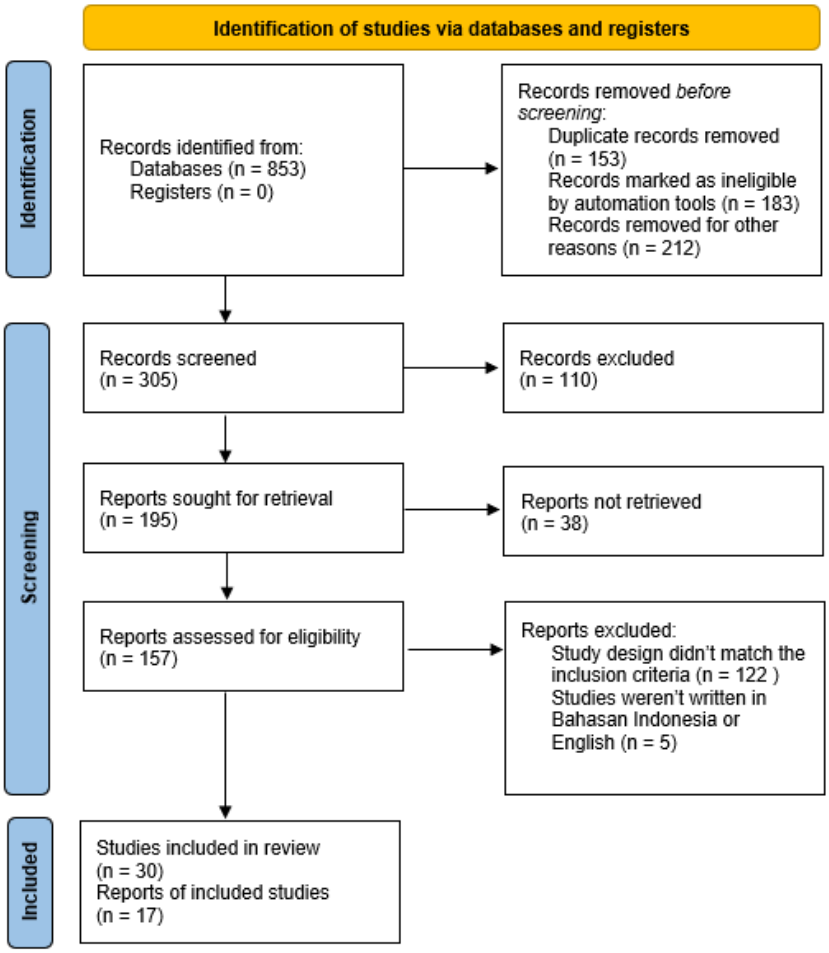

Figure 1. PRISMA flowchart.

Quality Appraisal

All studies used as literature in this study were assessed for risk of bias using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool template [9]. The assessment of the presence of bias is based on the percentage of risk from “low” which indicates a low probability of bias, “some concerns” which indicates some concern, and “high” which indicates a high percentage of bias. There are 8 out of 18 studies that show "some concerns" in the title or year of publication or discussion, but overall, all studies are still included in the "low" bias. So overall, we conclude that the 18 studies used in the literature have a low risk of bias. The results of the assessment can be seen in Figure 2 and Figure 3.

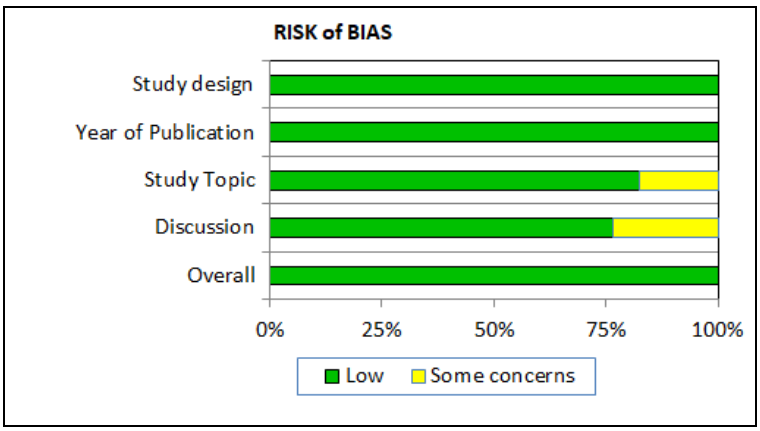

Figure 2. Distribution of the risk of bias judgments within each domain.

	Risk of bias				
	Study design	Year of Publication	Study Topic	Discussion	Overall
Chang, et al. (2020)	+	+	+	+	+
Kuban, et al. (2021)	+	+	+	+	+
Balestrini, et al. (2018)	+	+	+	+	+
Khalyfa, et al (2019)	+	+	?	+	+
Torabian, et al. (2019)	+	+	+	+	+
Dagenais, et al. (2017)	+	+	+	+	+
Quignot, et al. (2021)	+	+	?	?	+
Kam, et al. (2020)	+	+	+	+	+
Orsini, et al. (2018)	+	+	+	+	+
Božina, et al. (2019)	+	+	+	+	+
Galindo, et al. (2018)	+	+	+	+	+
Balestrini, et al (2017)	+	+	+	+	+
Patocka, et al. (2020)	+	+	?	+	+
Shah, et al. (2018)	+	+	+	+	+
Pratt, et al. (2019)	+	+	+	?	+
Cucchiara, et al. (2021)	+	+	+	?	+
Reddigari, et al. (2020)	+	?	+	+	+

Figure 3. The plots of the domain-level risk of bias judgments for each study.

Findings of the Review

We describe narratively and conclude 18 studies selected as literature relevant to the association between CYP2C9 and CYP2C19 polymorphisms, metabolism, and neurotoxicity following phenytoin administration in epilepsy patients. Based on the study literature used, we conclude that CYP2C9*2 and CYP2C9*3, and CYP2C19*3 polymorphisms can lead to decreased

phenytoin metabolism which can increase the risk of neurotoxicity in epilepsy patients due to increased phenytoin concentrations. The studies used in detail are summarized in **Table 1.**

Table 1
Main Findings of Each Study

Author (Year)	Study design	Study Topic	Main Finding
Chang, *et al*. (2020)	Review	CYP2C9 polymorphisms and phenytoin metabolism	CYP2C9 polymorphism increases the concentration of phenytoin which can cause side effects such as neurotoxic
Kuban, *et al*. (2021)	Review	The effect of polymorphism on the use of phenytoin	Phenytoin is influenced by CYP2C9 gene polymorphisms, especially in patients with slow metabolism of CYP2C9
Balestrini, *et al*. (2018)	Review	Personalized treatment for the epilepsies	CYP2C9 allele exhibits slower phenytoin metabolism rates at a greater risk of neurotoxicity
Khalyfa, *et al* (2019)	Review	The development of epilepsy has been associated with single or multiple gene variants	CYP2C19 genetic polymorphism affects the metabolic clearance of phenytoin contributing to the efficacy and safety
Torabian, *et al*. (2019)	Review	The genetic generalized epilepsy	Phenytoin metabolizes at a slower rate due to the CYP2C9 polymorphism followed by a significant increase in neurotoxicity
Dagenais, *et al*. (2017)	Review	Impact of Genetic Polymorphisms on Phenytoin	CYP2C9*1/*3 and CYP2C19*2 genotypes were significantly more likely to experience phenytoin-induced neurologic toxicity
Quignot, *et al*. (2021)	Review	Inter-phenotypic differences in CYP2C9 and CYP2C19 metabolism	CYP2C9 and CYP2C19 polymorphisms may affect their efficacy and safety including neurotoxicity associated with changes in phenytoin concentrations
Kam, *et al*. (2020)	Review	Pharmacogenomics in psychiatry for personalized pharmacotherapy	Poor CYP2C9 and CYP2C19 metabolism affect serum phenytoin concentrations, which may increase the risk of side effects
Orsini, *et al*. (2018)	Review	Personalized medicine in epilepsy patients	CYP2C9*2 and CYP2C9*3 polymorphisms lead to lower phenytoin clearance, higher serum phenytoin concentrations, and risk of central nervous system side effects
Božina, *et al*. (2019)	Cross-sectional	Pharmacogenetics and the treatment of epilepsy	CYP2C9 and CYP2C19 polymorphisms lead to an increased risk of neurotoxicity of phenytoin
Fricke-Galindo, *et al*. (2018)	Review	Pharmacogenetics of adverse reactions to antiepileptic drugs	CYP2C9 and CYP2C19 polymorphisms are associated with different ADRs, mainly neurologic effects

Author (Year)	Study design	Study Topic	Main Finding
Balestrini, *et al* (2017)	Review	Pharmacogenomics in epilepsy	CYP2C9 polymorphism causes a much slower metabolism of phenytoin and has a greater risk of causing neurotoxicity
Patocka, *et al*. (2020)	Review	Pharmacology and Toxicity of Phenytoin	CYP2C9 polymorphisms increase the frequency of cerebellar atrophy after phenytoin use
Shah, *et al*. (2018)	Review	Precision medicine related to genotype-based prescribing	CYP2C9*3 allele and CYP2C19 polymorphism are associated with a high risk of phenytoin-induced neurologic toxicity
Pratt, *et al*. (2019)	Experimental	Treatment recommendations with CYP2C9 genotypic allele changes	CYP2C9*6 allele has a lower frequency than other alleles with zero activity and its association with central nervous system phenytoin toxicity
Cucchiara, *et al*. (2021)	Review	Pharmacokinetic and pharmacodynamic interactions between alkylating agents and antiepileptic drug	Phenytoin was metabolized by the enzymes CYP2C9 and CYP2C19, the use of concentrations above 30 mg/L can show side effects including on the central nervous system
Reddigari, *et al*. (2020)	Case-control	CYP2C9 polymorphisms are associated with phenytoin toxicity	CYP2C9*2 and CYP2C9*3 allele variants most commonly result in a significant decrease in the metabolism of various CYP2C9 substrates and an increase in phenytoin toxicity, the most common clinical findings were ataxia and nystagmus

DISCUSSION

Epilepsy and Antiepileptic drug

Epilepsy is a neurological disorder that affects around 50 million people every year with a percentage of 1-3% of the general population which can be suffered by both men and women with a higher prevalence of men than women and all ages [10, 11]. ILAE (International League Against Epilepsy) defines epilepsy as a chronic neurological disease with symptoms of recurrent seizures characterized by the occurrence of one unprovoked seizure with a high probability of recurrence, two or more unexplained seizures occurring > 24 hours, long-standing brain disturbances causing disturbances neurobiologically, cognitively, psychologically, and socially due to epileptic seizures which are characterized by recurrent paroxysmal attacks which can be caused by excessive brain activity resulting in physical and behavioral changes such as confusion, loss of consciousness, and disturbing uncontrollable movements daily activities [10-12].

Most (about 50%) cases of epilepsy have no known cause, but epilepsy can also occur due to traumatic brain injury from perinatal causes, genetic factors, developmental disorders, infections, brain tumors, or even stroke [11]. Epilepsy in children is most commonly due to prenatal injuries that cause brain damage in children; traumatic brain injury; genetic conditions related to brain defects; hypoxic injury to the brain due to stroke; other diseases such as meningitis, encephalitis, neurocysticercosis due to central nervous system infection; brain tumor; and some genetic syndromes [10]. Epilepsy can generally be classified according to: (a) etiology; (b) clinical features of the seizure episode; (c) temporal patterns; (d) the

anatomical location of origin of the seizure; (e) the tendency to spread to other parts of the brain [10]. Assessment of the frequency and duration of seizures is necessary to assess the severity of epilepsy. In addition, several factors such as drugs (eg combinations of other drugs, surgery), the effects of seizures, and side effects arising from treatment also need to be considered [11].

Epilepsy is often treated with anti-epileptic drugs (AEDs) with several mechanisms of action, namely: (1) regulation of voltage-gated sodium channels (VGSCs) (e.g., carbamazepine, phenytoin), voltage-gated potassium channels (VGPCs) (e.g., retigabine), or voltage-gated calcium channels (VGCCs) (e.g., ethosuximide); (2) augmentation of inhibitory neurotransmission via gamma-aminobutyric acid type A (GABAA) receptors (e.g., benzodiazepines, tiagabine); (3) presynaptic terminal changes to regulate neurotransmitter release (eg, gabapentin, levetiracetam); and (4) glutamate receptors for reduced excitatory neurotransmission (e.g., perampanel) [11].

Although treatment with anti-epileptic drugs can control the incidence of epilepsy, the response to antiepileptic treatment varies greatly, depending on the patient because of genetic variations in the genes that cause or are associated with epilepsy [12]. The genetics of epilepsy usually involves interactions between several or many genes and is complex. If a genetic epileptic disorder is present, the patient will exhibit significant genetic heterogeneity, variable penetration, and seizure expressivity [10]. Individualized approaches to drug selection and more relevant epilepsy treatment can be detected through pathophysiological and molecular mechanisms. If the genetics of the disease are known, then the treatment can be adjusted according to the patient's metabolic correction so that the genetics of the disease can help select the appropriate anti-epileptic drug without exacerbating the situation and causing toxicity [13].

Fluctuating drug concentrations in the blood can increase due to increased individual genetic variation due to comorbidities. At the pharmacokinetic and pharmacodynamic levels, drug interactions can occur and can produce antagonistic or synergistic effects. Induction or inhibition of drug metabolism is one of the pharmacokinetic interactions that can occur due to the presence of other antiepileptic drugs which can reduce the efficacy of the drugs if given together because they are strong inducers of enzymes that metabolize other drugs that are taken simultaneously so that they can cause toxic side effects [10].

Phenytoin

Phenytoin is an aromatic ring compound is a fixed antiepileptic drug (AED) for chronic seizure prevention and acute management which has been widely used, especially in the treatment of focal and tonic-clonic seizures [1, 14, 15]. Its main mechanism of action is to reduce sodium influx into neurons via binding to inactive sodium channels potentially reducing neuronal hyperexcitability and prolonging periods of neuronal depolarization that inhibit neuron generation [1, 14]. Phenytoin is believed to increase levels of -aminobutyric acid (GABA) and the inhibitory neurotransmitter serotonin (5-HT) in the brain stabilizing the function of brain cell membranes [1].

Phenytoin is used prophylactically in neurosurgery by approximately 18% of people with epilepsy and has been identified for neurological, psychiatric, and non-CNS indications [1]. Individual patient genetic variation, type, and severity of epilepsy influence the dose of phenytoin to be used, with the generally recommended daily oral dose range for adults ranging from 300-400 mg, whereas in children the recommended initial dose of phenytoin is usually given 2-3 times a day as much as 5 mg/kg BB [14].

Phenytoin is mostly bound to protein (90%), especially albumin, where the unbound form has pharmacological activity. Phenytoin pharmacokinetics shows zero-order or non-linear pharmacokinetics so therapeutic concentrations are difficult to achieve [14]. The therapeutic window for phenytoin is narrow, with a recommended therapeutic window range of 40–80 mol/L (10–20 μg/mL) in adults and 8–15 g/dl in neonates or children, in which range phenytoin

will reach concentrations optimally without side effects [1, 15]. However, the highly variable inter-patient variability makes it difficult to achieve the optimum dose-response and concentration of the given dose [15].

Several side effects and toxicity have been attributed to excessive doses of phenytoin, which can induce peripheral neuropathy, cause dyskinesia, and cerebellar dysfunction due to central nervous system inhibition [14]. Hand tremor (mean plasma concentration 20 µg/mL), nystagmus, ataxia (mean plasma concentration 30 µg/mL), and diplopia depending on blood concentration of phenytoin are manifestations of the phenytoin-induced cerebral syndrome; At an average phenytoin plasma concentration of 40 µg/mL or more, it can cause coma [1]. In addition, several other factors such as serum albumin levels, comorbidities, patient body composition, and interactions with other drugs can influence patient-to-patient variability in the effects of phenytoin used [15]. In addition, genetic polymorphisms of enzymes and transporters are significant contributors to inter-patient variability and influence the pharmacokinetics of phenytoin [15].

CYP2C9 and CYP2C19 are hepatic cytochrome P450 (CYP) enzymes which are the main metabolizing enzymes of phenytoin. The hydroxylation pathway of phenytoin to form 5-(4'-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) is the main pathway that eliminates about 80% of phenytoin to its inactive form and is excreted via the kidneys [14]. Hydroxylation can stimulate immune reactions, cause cell damage, and thus cause hypersensitivity or toxicity. However, the arene oxide intermediates still do not have a definite functional role due to their unstable structure [14]. Phenytoin metabolism can be affected by the cytochrome P450 (CYP) 2C9 polymorphism, so based on the genotype, it is necessary to adjust the dose of phenytoin. In addition, there is evidence that CYP2C19 polymorphisms can also significantly affect phenytoin concentrations and require dose adjustment [15].

Phenytoin Metabolism

The metabolism of antiepileptic drugs in humans is largely mediated by the cytochrome P450 (CYP) family. CYP enzymes can have genetic variants (alleles) that code for different isoform activities, polymorphisms can affect antiepileptic drug serum concentrations if they occur in genes that code for drug-metabolizing enzymes and potentially increase the risk of subsequent drug toxicity [16], [17]. Polymorphisms of CYP2C9 and CYP2C19 enzymes produce allelic variations that can cause large differences in serum concentrations of antiepileptic drugs [17]. 90% of the total metabolism and elimination of phenytoin is carried out by the CYP2C9 enzyme as the main metabolic enzyme. Genetic polymorphism in CYP2C9 alters the activity of the enzyme encoding variant enzyme (allozyme) exhibiting a slower metabolic rate of phenytoin due to reduced activity compared to individuals homozygous for the wild-type allele and consequently affecting plasma phenytoin levels and having a greater risk of neurotoxicity due to increased phenytoin concentrations [14, 17].

Several pharmacogenetic studies have shown that polymorphisms in the CYP2C9 and CYP2C19 enzymes can each determine the kinetics of phenytoin [18]. The CYP2C9 enzyme has at least alleles *1 to *61 which are 60 identified star variants (*) that are highly polymorphic [17]. The *1 allele in CYP2C9*1 wild type is a homozygous carrier that is considered to have normal enzyme activity so that the metabolism is normal (normal metabolizer), where 90% of the patient population is represented by this allele [14].

Genetic polymorphisms in CYP2C9*2 and CYP2C9*3 are variants with one or two copies of the most common functional variant *2 or *3 that are classified as poor or intermediate metabolizers [14]. A 29% decrease in phenytoin clearance resulted from the CYP2C9*2 allele when compared to CYP2C9*1 while CYP2C9*3 resulted in a more severe decrease in phenytoin clearance, 93-95% when compared to CYP2C9*1 so that the time of plasma phenytoin concentration shown by the bottom area curve (AUC) to be 4-5 times higher compared to normal metabolism [14]. CYP2C19 also metabolizes about 10% of phenytoin at a much lower rate than CYP2C9 [18]. It has been reported that various CYP2C19*2 and

CYP2C19*3 enzyme polymorphisms can affect plasma phenytoin levels and increase phenytoin toxicity in some populations [18, 19]. The average maximal elimination rate (Vmax) in patients with the CYP2C9*1/*3 genotype is 30-40% lower compared to patients with normal metabolism resulting in higher plasma concentrations, so dose adjustment is necessary for patients with low metabolism [14].

Polymorphism

Genetic mutations can change the response to antiepileptic drugs pharmacokinetically such as drug-metabolizing enzyme polymorphisms and at a good pharmacodynamic level such as drug target polymorphisms [19]. Phenytoin is metabolized by two main enzymes, 90% of phenytoin metabolism is responsible for CYP2C9 enzymes, while the remaining 10% is responsible for CYP2C19 [18, 19]. Changes in the pharmacokinetic profile of phenytoin can affect its efficacy and safety so polymorphisms in genes encoding cytochromes are reported to cause side effects of different drugs, especially neurological effects related to changes in phenytoin. concentration [20-22]. Modification of the expression of enzymes involved in the pathogenesis of pharmacoresistant and other molecules or mutations in genes that cause epilepsy are some other mechanisms that may be involved in the safety and efficacy of therapy [19]. The use of phenytoin at concentrations above 30 µg/mL due to impaired polymorphism of metabolic enzymes can show side effects including on the central nervous system [23].

CYP2C9 Polymorphism

The hepatic cytochrome P450 enzymes (CYP2C9) metabolize most of the phenytoin, accounting for 90% of its metabolism, if CYP2C9 polymorphism occurs, it causes decreased enzyme activity in some individuals, resulting in higher serum phenytoin concentrations due to lower phenytoin clearance and causes side effects in the central nervous system with a greater risk in persons experiencing the polymorphism [19]. CYP2C9 polymorphisms are associated with decreased cerebellar volume in epileptic patients taking phenytoin. In addition, CYP2C9 gene polymorphism with a slow metabolism variant also affects the duration of treatment of focal seizures using phenytoin [24].

Polymorphism is considered to be a major determinant of the metabolic rate of phenytoin. Variant alleles of the CYP2C gene namely CYP2C9*2 and CYP2C9*3 of the CYP2C gene are the two most common allelic variants that will result in slower and significantly decreased phenytoin metabolism with significantly increased concentration-based neurotoxicity [25-27]. Patients with the CYP2C9 allele polymorphism may have impaired metabolism of phenytoin and require dose adjustment to prevent toxic neurological effects [28]. It has been reported that phenytoin-induced CYP2C9*3 alleles carry a high risk of neurologic toxicity in epilepsy patients in India, but in African Americans and their offspring, variants of the CYP2C9*5, *6, *8, and *11 alleles pose a risk of neurologic toxicity. , but the CYP2C9*6 allele has a lower frequency than the other alleles [28, 29]. In addition, the risk of neurologic toxicity may also be exacerbated in patients with polymorphisms or impaired CYP2C19 enzyme activity which also contributes to phenytoin metabolism [29].

The CYP2C9*2 polymorphism shows 12% lower enzymatic activity or metabolism than the CYP2C9*1 wild type, whereas the decrease in enzymatic activity at the CYP2C9*3 allele is only about 5% of CYP2C9*1 wild type indicating that drug concentrations can be very high. if this polymorphism occurs [21]. In Tamil patients, the CYP2C9*2 and *3 allele frequency polymorphisms had higher toxicity compared to patients who did not experience phenytoin toxicity [4]. In addition, the frequency of occurrence of these enzyme polymorphisms depends on the particular population type, the frequency of polymorphisms for the CYP2C9*2 allele is about 16%, and for CYP2C9*3 is 10% in the Spanish population, while the frequency is lower in African-American, Chinese and Mexican populations [21]. Two alleles related to CYP2C9 enzyme polymorphism studies with reduced enzyme activity were identified in the African-

American population, namely, the CYP2C9*6 (c.delA818) and CYP2C9*5 (Ile359Thr) alleles, which exhibit a poor metabolic phenotype to phenytoin, which can lead to neurotoxicities such as ataxia, nystagmus, dizziness, altered level of consciousness, excessive sedation, and confusion, but can also have a negative impact on medication adherence and patient quality of life [21].

CYP2C19 Polymorphism

Genetic polymorphisms to the CYP2C19 enzyme are associated with variable drug responses of clinical relevance because they affect the metabolic clearance of the drug and contribute to the variability in pharmacodynamics regarding drug efficacy and safety so that based on the metabolic ability of the CYP2C19 enzyme, epilepsy patients can be classified into several types [10]. The genotype of CYP2C19 influences phenytoin metabolism, although not playing a major role such as CYP2C9 [21]. Increased CYP2C19 activity is associated with depression, decreased hippocampal volume, and impaired homeostasis [24]. Several CYP2C19 enzyme-reduced allele variants (*2, *3, *4) can lead to poor metabolizer phenotypes due to reduced enzyme activity and potentially increase the toxic effects of phenytoin use. In addition, there is the CYP2C19*17 allele which is the largest inter-ethnic diversity that can cause increased enzyme activity (ultrarapid metabolizer) and is responsible for the phenotype of fast and very fast metabolism so that drug concentrations are lower in plasma. and hence the desired therapeutic effect is not achieved [20, 29].

The most common allele of the CYP2C19 enzyme is the CYP2C19*2 allele with an allele frequency of around 29-35% in Asians, 15% in African Americans, and 12% in Caucasians [10]. In Mediterranean-Southern European populations, the allele is CYP2C19*17 more common with 42-fold frequency and in Middle Eastern populations it is 24-fold more common than in East Asia, where the alleles are CYP2C19*2 and CYP2C19*3 alleles [29]. Individuals who are intermediate metabolizers (IM) are derived from the wild-type allele (CYP2C19*1). Decreased phenytoin hydroxylation in vivo occurs in CYP2C19*2 and *3 mutant alleles, but the CYP2C19 mutant allele plays only a minor role in phenytoin metabolism [10].

The intermediate metabolizer genotype results in reduced CYP2C19 enzyme activity, in that the gene consists of one variant allele encoding reduced enzyme function and one wild-type allele (e.g., *1/*2, *1/*3), whereas two alleles that are abrogated result in very low or no CYP2C19 activity (poor metabolizer)(e.g., *2/*2, *2/*3, *3/*3). The resulting increase in enzyme activity and expression on the CYP2C19*17 allele is the site of the SNP on CYP2C19 (rs12248560), which creates a GATA transcription factor binding site with a C > T transition in the promoter [10].

Phenytoin pharmacokinetics was not significantly affected by the CYP1C19*2 and *3 allele variants. In addition, due to the non-functional nature of the *2 allele, significantly different serum phenytoin concentrations were not associated with CYP2C19*1/*2 and *2/*2 genotypes. However, clinical statistical differences are likely to emerge after repeated doses of phenytoin. A decrease in functional effectiveness has a significantly lower effect on serum phenytoin concentrations when compared to a decrease in function of the variant CYP2C9 enzyme alleles because phenytoin metabolism occurs only 10–30% with CYP2C19 enzymes [15], [30].

CONCLUSION

Based on the literature of 18 studies, we found that there was an association between CYP2C9 and CYP2C19 polymorphisms, metabolism, and the incidence of neurotoxicity following phenytoin use in epilepsy patients. Polymorphism of CYP2C9 to the allele forms CYP2C9*2 and CYP2C9*3 can decrease phenytoin metabolism seen in certain populations, generally decreasing metabolism to 12% and 5% in the general population, respectively. In addition, in the African-American population, two alleles can cause decreased activity of CYP2C9 enzymes (CYP2C9*5 and CYP2C9*6). A small part of phenytoin metabolism can also be

affected by CYP2C19 enzymes with CYP2C19*2 and CYP2C19*3 alleles. CYP2C9 polymorphism has a significant effect on serum phenytoin concentrations, causing neurotoxic side effects that can be used at drug concentrations, while CYP2C19 polymorphism has no significant effect on phenytoin pharmacokinetics, but can increase if repeated doses are used. In addition, the CYP2C19 polymorphism is also the serum concentration of phenytoin in patients with the CYP2C9 polymorphism, but this is less common. Therefore, it is necessary to adjust the dose for patients with CYP2C9 and/or CYP2C19 polymorphisms to prevent neurotoxic side effects.

AUTHOR'S CONTRIBUTION

All authors are responsible for contributing to the development and writing of this article.

CONFLICT OF INTEREST

The authors declare no conflict of interest in the study.

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