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PharmGKB summary: phenytoin pathway

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Keywords

CYP2C19, *CYP2C9*, *HLA-B*; pathway; pharmacogenomic; pharmacokinetics; phenytoin; *SCN1A*

Background

Phenytoin is one of the most widely prescribed antiepileptic drugs (AEDs) in the USA (approximately 52% of AED prescriptions compared with 19% for valproic acid, 11% carbamazepine, and 7% phenobarbital) [1]. It has a narrow therapeutic range and wide interindividual variability in clearance and, as such, therapeutic drug monitoring is often necessary. Adverse effects of phenytoin range from minor (e.g. gingival hyperplasia) to severe and life threatening [e.g. Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)], and teratogenic (e.g. birth defects).

Pharmacokinetics

Metabolizing enzymes

Phenytoin is primarily metabolized to the inactive hydroxyphenytoin, 5-(4'-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH) (Fig. 1) [2]. Up to 90% of phenytoin is metabolized to *p*-HPPH and then glucuronidated and excreted into the urine [3]. Two stereoisomers of *p*-HPPH are formed: (R)-*p*-HPPH and (S)-*p*-HPPH and there is considerable interindividual variation in the relative amounts [4,5]. When the reaction is catalyzed by CYP2C19, the ratio of (R)-*p*-HPPH and (S)-*p*-HPPH is approximately 1 : 1 [6]. However, when the reaction is catalyzed by CYP2C9, the ratio favors formation of the S isomer by as much as 40 : 1 [4,6]. Thus, the relative ratios of stereoisomers can be used to phenotype genomic variants of *CYP2C9* and *CYP2C19*.

Formation of *p*-HPPH is thought to proceed through a reactive arene oxide intermediate [7], and the 'arene oxide hypothesis' has been the prevailing mechanism cited by most authors reporting cases of phenytoin hypersensitivity reactions, SJS/TEN, hepatotoxicity and other forms of idiosyncratic toxicity. The arene oxide can also be converted to phenytoin dihydrodiol through epoxide hydrolase, *EPHX1* [2]. Formation of the dihydrodiol has been

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Conflicts of interest

There are no conflicts of interest.

shown *in vitro* also to be catalyzed by CYP1A2, CYP2C19, CYP2E1, CYP2A6, CYP2D6, CYP2C8, CYP2C9, and CYP3A4 [8]. The dihydrodiol metabolite can also be converted to the catechol [2].

Hydroxyphenytoin can be converted to a catechol, 3'-4'-diHPPH, by several P450 enzymes. CYP2C19 was found to be the most effective catalyst of catechol formation, however, CYP2C9 and CYP3A4 may be responsible for the majority of the transformation because of their relative predominance in the liver [8,9]. CYP3A5, CYP3A7, CYP2D6, and CYP2B6 were also shown to catalyze the catechol formation to some extent *in vitro* [8,9]. Although because of the limited expression in liver, CYP2C18 is reported to be expressed in the skin and has been shown to catalyze the primary and secondary hydroxylation steps [10] that may be of relevance to cutaneous adverse drug reactions (ADRs).

The catechol spontaneously oxidizes to form a reactive quinone metabolite that can be metabolized back to the catechol by NQO1. The catechol can also be metabolized to the methylcatechol by COMT, which is then eliminated in the urine [2].

Hydroxyphenytoin is glucuronidated by uridine 5'-diphospho-glucuronosyltransferase (UGTs), specifically UGT1A1, UGT1A4, UGT1A6, and UGT1A9. It has been proposed that this glucuronidation prevents a peroxidase-mediated conversion of hydroxyphenytoin to a toxic reactive metabolite that can oxidize proteins, lipids, and DNA [11]. Glucuronidation of *p*-HPPH is stereoselective with UGT1A1 glucuronidating the S isomer preferentially and UGT1A9 and UGT2B15 acting on the R isomer [3].

ADRs to phenytoin generally fall into two categories: dose-dependent (or concentration-dependent) toxicities and hypersensitivity reactions that are idiosyncratic in nature. As discussed in more detail, concentration-dependent ADRs are associated with impaired *p*-hydroxylation and excessive accumulation of phenytoin. There is still some debate as to which forms of the drug and its metabolites are most often involved in generating hypersensitivity reactions. Phenytoin and *p*-HPPH have been shown to form adducts with a variety of endogenous enzymes [10]. Antibodies recognizing CYP3A4, PTGIS, and TBXAS1 have been observed in the serum of hypersensitive patients [2].

Transport

The most widely discussed transporter for phenytoin is *ABCB1*. *ABCB1* has been shown *in vitro* to transport phenytoin across gradient in cell lines [12-14]. The action of *ABCB1* at the blood-brain barrier has been suggested as a mechanism of resistance to AEDs including phenytoin. Various studies have looked at the role of *ABCB1* variants on resistance (see Pharmacogenomics section). *ABCB1* has shown to be overexpressed in the epileptic brain [3]. COX-2 inhibitors have been shown to decrease epilepsy-related upregulation of *ABCB1* and improve brain transport of phenytoin preventing resistance in animal models [15].

Experiments in rats suggest a role for *ABCC2* in transporting phenytoin across the blood-brain barrier [16], but in-vitro cell line studies did not support transport of phenytoin through *ABCC1*, *ABCC2*, or *ABCC5* [17].

Pharmacodynamics

Phenytoin targets voltage-gated sodium channels in the brain [18,19]. Voltage-gated sodium channels are heteromeric complexes consisting of a large glycosylated α subunit (approximately 260 kD) and two smaller β subunits (33–39 kD). The voltage-gated sodium channels are coded for by the *SCN* family of genes, which has members expressed in the heart and skeletal muscle as well as the peripheral and central nervous systems. The genes

SCN1A, *SCN2A*, and *SCN3A* code for the α subunits expressed in the brain [20]. Mutations in *SCN1A* are associated with epilepsy; over 500 variants have been reported, including those associated with Dravet syndrome also known as severe myoclonic epilepsy of infancy [21]. Epilepsy-associated variants have also been reported in *SCN2A* but few variants in *SCN3A* have been documented [21].

Phenytoin binds the *SCN2A* channel preferentially in the open formation [19]. It is thought that phenytoin blocks sodium channels poorly at slow firing rates allowing normal brain activity but suppresses the high-frequency repetitive firing characteristic of seizures [19,22]. Variants in the sodium channels could therefore impact phenytoin efficacy.

Pharmacogenomics

Several studies have reported associations between genomic variation and dose, metabolic ratios or plasma drug levels; relatively few have explored their roles in drug resistance and ADRs. Most studies have examined the role of *CYP2C9* with a small number examining other metabolizing enzymes, transporters, and pharmacodynamic candidate genes.

Metabolizing enzyme variants

Impaired phenytoin *p*-hydroxylation was first reported in 1964 [23] and is characterized by increased phenytoin concentrations, prolonged elimination half-lives and signs of intoxication—nystagmus, ataxia, and impaired consciousness [24–26].

*CYP2C9**3 (rs1057910 A > C) is associated with decreased metabolism of phenytoin *in vitro* and *in vivo* in pharmacokinetic studies of epileptic patients [4,9,27]. *CYP2C9**3 is also associated with increased dose in patients with epilepsy [28]. Studies of the *CYP2C9**2 (rs1799853 C > T) variant have had contradictory results. *CYP2C9**2 was associated with decreased metabolism in patients with epilepsy in a North American study [4] but not associated with metabolism *in vitro* or phenytoin dose in a study of white epileptics [9,28]. This discrepancy may be explained by additional variants in the *CYP2C9* promoter that are in linkage with *CYP2C19**2 [1]. The A allele of rs12782374G > A and deletion allele of rs71486745T > del are associated with decreased dose of phenytoin in people with epilepsy [1]. Additional *CYP2C9* variants which are present in black populations, *CYP2C9**5, *6, *8 and *11 but not *CYP2C9**9, are associated with a decreased phenytoin metabolism [29].

A recent study of Asian Indians that showed increased free phenytoin in the plasma of *CYP2C9**3 carriers also showed increased risk for concentration-dependent toxicity compared with *1 homozygotes [27]. This study also showed increased free phenytoin in plasma of *CYP2C9**2 carriers but heterozygotes did not have significantly increased risk of drug toxicity. However, the one homozygous *CYP2C9**2 individual in this study showed increased risk for drug toxicity [27]. This study also noted that phenytoin metabolism was impaired in under-nourished individuals and effects of *CYP2C9* variants were more evident. A small study (*n* = 14) of cases of phenytoin toxicity in Americans (all cases were white) showed increased risk for the *CYP2C9**1*3 and *CYP2C9**2*2 genotypes, although these were not significant [30].

Few studies have examined the pharmacogenetic effects of genes other than *CYP2C9*. A study of *CYP2C19* rs4244285 (present in the *2 allele) in epileptic patients showed decreased phenytoin metabolism in heterozygotes compared with *1 homozygotes [4]. No reports of *CYP2C19* variant effects on drug efficacy nor toxicity have been observed to date, although a couple of studies have reported effects from other pharmacokinetic candidate genes on clinical outcomes. The *CYP1A1* rs2606345 A allele is associated with increased risk of seizures in epileptic women when treated with carbamazepine, phenobarbital,

phenytoin or valproic acid as compared with the C allele [31]. However, this association was not seen in men. Two maternal SNPs in *EPHX1* (rs2234922 G and rs1051740 T) were associated with the risk of craniofacial abnormalities in women exposed to phenytoin during their first trimester of pregnancy [32].

Transporter variants

Some evidence suggests that the well-known *ABCB1* variant 3435C > T rs1045642 affects plasma drug levels and drug resistance. A haplotype of three *ABCB1* variants including rs1045642 altered phenytoin-inhibited transport of marker substrates *in vitro* [14]. In another study, a different haplotype containing the rs1045642 T allele was associated with increased plasma drug levels in healthy black African volunteers [29]. Both haplotypes also contained 1236C > T (rs1128503). In a study of British epileptics in which specific AEDs were not defined, rs1045642 CC genotype was associated with drug resistance [33]. In addition, a study of Egyptian epileptics showed increased likelihood of resistance to phenytoin in C allele carriers [34]. Further studies, including a meta-analysis [35], have failed to replicate the association with rs1045642, although many of these studies comprised patients on a variety of AEDs rather than phenytoin alone. The studies included in the meta-analysis were also analyzed in subgroups of white and Asian cohorts and the overall results were still negative; however, they did not look at studies of black or African Americans where different haplotypes may have had an impact.

Pharmacodynamic variants

There have been a few studies of candidate genes in the pharmacodynamics of phenytoin. The T allele of *SCN1A* rs3812718 is associated with increased dose of phenytoin in people with epilepsy as compared with allele C [28,36]. In-vitro studies support this association, demonstrating that rs3812718 affects alternative splicing of the NaV1.1 coded for by *SCN1A*. The C allele is associated with increased expression of splice variant Na(V) 1.1–5 N, whereas the TT genotype is associated with almost no expression of Na(V) 1.1–5 N only Na(V) 1.1–5A [37]. The NaV1.1–5N splice variant channel is associated with increased sensitivity to phenytoin compared with the NaV1.1–5A splice variant channel [38].

The *SCN2A* SNP rs2304016 A allele is associated with drug resistance to AEDs including phenytoin in Chinese epileptics [39].

Major histocompatibility locus variants

Although more readily studied with respect to another AED carbamazepine, major histocompatibility locus variants have also been investigated for their role in phenytoin-induced ADRs. The most well-studied variants are highly complex haplotypes spanning the *HLA-B* gene and surrounding region that correspond to serotype phenotypes and may be tagged by different SNPs in different populations. The *HLA-B*1502* allele has been associated with severe ADRs in response to carbamazepine in several Asian populations (see Carbamazepine Pathway for details at PharmGKB: <http://www.pharmgkb.org/do/serve?objCls=Pathway&objId=PA165817070>).

The *HLA-B*1502* allele was associated with phenytoin-induced SJS in a Thai population [40], and was also associated with phenytoin-induced SJS and TEN in Chinese Asian population [41]. Additional MHC locus alleles *HLA-B*1301*, *Cw*0801*, and *DRB1*1602* also showed an association with phenytoin-induced SJS/TEN in Han Chinese [41].

Conclusion

The pharmacokinetics of phenytoin is fairly well studied and the impact of genomic variation on plasma drug levels and metabolism has been studied in healthy populations and patients with epilepsy. However, fewer studies have shown how these alterations in metabolism affect drug response, resistance, and ADRs. There is a need for studies that consider multiple variants and haplotypes and their effects in well-defined populations, preferably on phenytoin alone.

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Fig. 1. Stylized liver cell depicting candidate genes involved in the metabolism of phenytoin. A fully interactive version is available online at <http://www.pharmgkb.org/do/serve?objCls=Pathway&objId=PA145011115>.