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Review

Pharmacogenetics of the antiepileptic drugs phenytoin and lamotrigine

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Abstract

Patients treated with antiepileptic drugs can exhibit large interindividual variability in clinical efficacy or adverse effects. This could be partially due to genetic variants in genes coding for proteins that function as drug metabolizing enzymes, drug transporters or drug targets. The purpose of this article is to provide an overview of the current knowledge on the pharmacogenetics of two commonly prescribed antiepileptic drugs with similar mechanisms of action; phenytoin (PHT) and lamotrigine (LTG). These two drugs have been selected in order to model the pharmacogenetics of Phase I and Phase II metabolism for PHT and LTG, respectively. In light of the present evidence, patients treated with PHT could benefit from *CYP2C9* and *CYP2C19* genotyping/phenotyping. For those under treatment with LTG, *UGT1A4* and *UGT2B7* genotyping might be of clinical use and could contribute to the interindividual variability in LTG concentration to dose ratio in epileptic patients.

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Pharmacotherapy of epilepsy

Epilepsy: definition and epidemiology

Epilepsy is a multifactorial disorder characterized by recurrent unprovoked seizures, which is the clinical manifestation of uncontrolled electrical activity by a group of neurons. Clinically, epilepsy is defined by the occurrence of two or more unprovoked seizures (1). The epilepsies affect approximately 50 million people worldwide, with an annual incidence of 50–70 cases per 100,000 in industrialized countries and this could be even much higher in developing countries (2). Thus, it approximately affects 1%–2% of the whole population, becoming the most prevalent chronic neurological affection (3, 4) and a problem of public health relevance in the world (5).

Pharmacological treatment

The goal of treatment with antiepileptic drugs (AEDs) is to attain seizure freedom without side effects and return patients to normal healthy lifestyles (6). Currently there are more than 17 drugs approved for the treatment of epilepsies. Among these, phenytoin (PHT) and lamotrigine (LTG) are two of the AEDs first line therapies. AED treatments are of relevance because they are shown to control seizures in up to 70% of patients in new onset epilepsy studies (7). Although major advances have been achieved in the pharmacotherapy of epilepsy, this is refractory to medical treatment in approximately 20%–30% of the patients (8). Four main limitations inherent to AEDs have been highlighted (9), in particular when using AEDs for long-term treatments. These include (a) AEDs are 'symptomatic' (antiseizure and not antiepileptogenic) agents; (b) AEDs have a suboptimal tolerability profile and can be teratogenic; (c) although second-generation AEDs have better pharmacokinetic profiles and are "better tolerated", they may not be overall more efficacious than the older drugs; (d) the choice of AEDs is made difficult by several factors that might differ across patients.

Interindividual variability in AEDs treatment response largely depends on multiple factors such as seizure type or epilepsy syndrome, optimal dosing, administration, concomitant diseases and treatments, lifestyle, physiology, metabolism and

age (10). This variability in clinical response limits AEDs clinical utility. However, the unpredictability of AEDs efficacy, the optimal doses and the induced adverse reactions could, at least in part, result from genetic variation (11). In fact, it has been estimated that genetic factors account for 20%–95% of patient variability in response to individual drugs (12). This genetic difference has a potential effect on the clinical efficacy of AEDs and can also affect the tolerability and safety of the drugs.

Additionally, pharmacokinetic variability appears to be prevalent for some of the newer AEDs; including LTG, as in many of the older AEDs. In keeping with this, a major focus of clinical research and dosage individualization to optimize drug treatment of epilepsy has been developed; measuring drug concentrations via therapeutic drug monitoring (TDM) (13, 14). Drug dosage must be adjusted to every patient not only to improve clinical response but to avoid adverse events. Thus, TDM and pharmacogenetics are two tools to be used for such dosage individualization in order to prevent AEDs lack of clinical efficacy or induced side effects.

AEDs have also been used beyond the treatment of seizure disorders since the 1960s. As new antiepileptic drugs appeared, there has been interest in how they compare with older therapies (PHT, carbamazepine, and valproate) and with regard to various disorders (i.e., bipolar disorder, fibromyalgia, migraine prophylaxis, and chronic pain), where conventional pharmacotherapy has typically been suboptimal and limited by drug-related toxicity (15). Among new AEDs, LTG has a wide therapeutic range. Since its approval by the FDA, LTG has gained monotherapy indications for partial seizures as well as for treatment of bipolar disorders (16).

The pharmacogenetics of the phenytoin and lamotrigine

The classic AED, PHT is related to the barbiturates in chemical structure but has a five-member ring. It was first introduced in 1938 and it is a major anticonvulsant drug that is used in a wide variety of seizures. It is also an anti-arrhythmic and a muscle relaxant. The mechanism of therapeutic action is not clear, although several cellular actions have been described, including effects on ion channels, active transport and general membrane stabilization. The mechanism of its muscle relaxant effect appears to involve a reduction in the sensitivity of muscle spindles to stretch.

The AED phenyltriazine class LTG was first introduced in 1986. LTG acts at voltage sensitive sodium channels (17) and inhibits release of excitatory neurotransmitters such as glutamate (18). LTG has been shown to be effective as monotherapy in newly diagnosed adolescents and adults with either partial or mixed seizure disorders and it is also effective for newly diagnosed absence seizures in children (19). After oral administration, LTG shows good absorption, a linear relation between dose and plasma concentration, and an elimination half-life of 25–30 h when administered as monotherapy (20). LTG elimination is mediated by hepatic glucuronidation catalyzed by UDP-glucuronosyltransferases (UGT)1A4 (21), UGT2B7 (22) and possibly UGT1A1 (23–25).

This review will focus on the aromatic antiepileptic drugs PHT and LTG as examples of an old and a new antiepileptic drug, in order to model pharmacogenetics Phase I and Phase II metabolism, respectively. PHT is metabolized primarily through hydroxylation by Phase I enzymes CYP2C9 and CY2C19, whereas glucuronidation by UGTs is the main pathway of LTG detoxification. Therefore pharmacogenetics of these two drugs as a model for Phase I and Phase II metabolism will be reviewed (Figure 1).

Moreover preventing and managing adverse effects is a major challenge in optimizing AED therapy. Factors that might affect the risk of adverse effects include: dosing frequency and rate of dose escalation, length of early tolerance development, and magnitude of peak serum concentrations (26). Therefore, dosage individualization in order to achieve

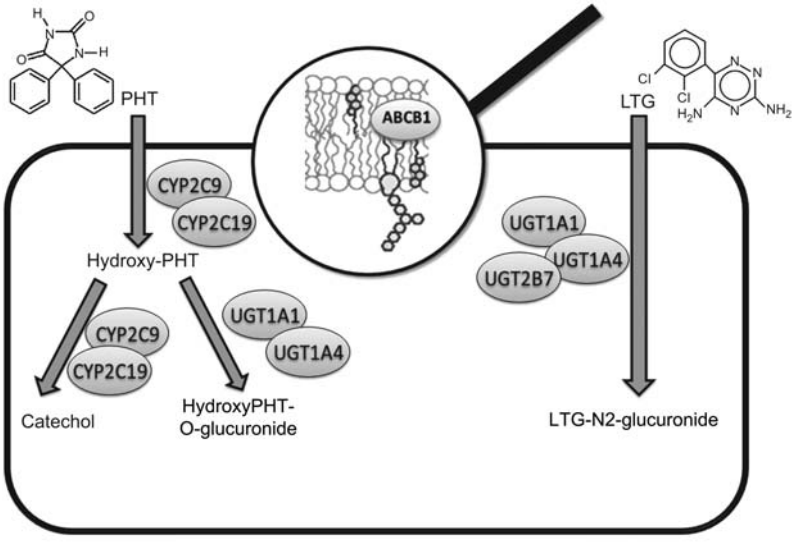

Figure 1 Main genes involved in the distribution and metabolism of phenytoin (PTH) and lamotrigina (LTG) in a human cell.

adequate plasma concentration might help to decrease clinically relevant drug side effects.

CYP2C9 and *CYP2C19* genetic polymorphism and PHT metabolism

CYP2C9 and *CYP2C19* genetic polymorphism

Genetic polymorphisms in cytochrome P450 (CYP) enzymes mainly affect the pharmacokinetics of drugs that are substrates for those enzymes. Genetically caused variability in drug metabolism is reflected in differences in clearance, half-life and maximal plasma concentrations (27, 28).

Cytochrome P450 genes (*CYP*) encode Phase I drug metabolizing hemoproteins that catalyze the oxidative metabolism of many endogenous substances and exogenous compounds, in addition to clinically used drugs. The *CYP2C9* and *CYP2C19* genes are members of the *CYP2C* gene cluster located on chromosome 10q24.1-q24.3, which include *CYP2C8*, –2C9, –2C18 and –*2C19*. At the present time, 34 and 28 sequence variants have been reported for *CYP2C9* and *CYP2C19*, respectively (29).

The gene encoding *CYP2C9* is highly polymorphic; it is expressed with more than 20 variant alleles. It has been reported that the major allelic variants, *CYP2C9*1* (wild-type), **2* and **3* might cause interindividual and interethnic variability in the disposition of its substrates. The frequencies of these genetic variations in *CYP2C9* have been described for Caucasian and Asian populations showing interethnic variability (30) (Table 1).

In a Spanish population, the frequencies of *CYP2C9*1, *2*, and **3* alleles were 0.74 (95% CI: 0.68–0.80), 0.16 (95% CI: 0.11–0.21) and 0.10 (95% CI: 0.06–0.15), respectively (31); however, a lower frequency of *CYP2C9*2* was found among Mexican-Americans (32). The authors hypothesized that the frequency of *CYP2C9*2* might be related to Amerindian ancestry. Later, they showed that among Mexican Tepehuanos the frequency of *CYP2C9*2* was lower than those of Mexican Mestizos and Spaniards, which was in agreement with such interethnic association (33). This could be of relevance for adjusting doses of CYP2C9 substrates according to ethnical background.

There are also interethnic differences in the frequency of *CYP2C19* alleles. The genetic polymorphism of *CYP2C19* was widely observed in Asian populations and the three polymorphic alleles *CYP2C19*1* (wild-type), *CYP2C19*2* and *CYP2C19*3* were identified among Chinese (30) and Japanese (34, 35) (Table 1).

Pharmacogenetics of PHT and its clinical implications

PHT is a narrow therapeutic index drug with non-linear pharmacokinetics that could be related to the implication of CYPs polymorphic enzymes in its metabolism. PHTs primary metabolic pathway is hydroxylation by CYP2C9 to 5-(4-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH). Approximately 95% of the *p*-HPPH produced by CYP2C9 has the (*S*) configuration. CYP2C19 is responsible for most of the (*R*)-*p*-HPPH formed (36) but this isoform usually plays a minor role in PHT hydroxylation unless the CYP2C9 pathway becomes saturated at higher doses of the drug (14, 37, 38).

The *CYP2C9*2*, *CYP2C9*3* and *CYP2C19*2* alleles affect the PHT plasma concentration and toxicity (14, 39). Several case studies reported that PHT induced central nervous system toxicities were observed when the patients were carriers of defective *CYP2C9* and/or *CYP2C19* allele(s) (14, 40, 41). Concerning the development of cutaneous adverse drug reactions (from exanthema to Stevens-Johnson's syndrome) or gingival hyperplasia during PHT therapy, it is not yet clear whether there is an association with *CYP2C9/2C19* polymorphisms (14, 42, 43).

A study in a Turkish population has shown significantly increased PHT levels and reduced p-HPPH/PHT ratios in individuals with *CYP2C9*1/*2*, **2/*2* and **1/*3* compared to **1/*1* genotypes (44). The maximal elimination rate (V_{max} of PHT is 33% lower in patients heterozygous for *CYPC9*1/*3* than in patients homozygous for *CYP2C9*1/*1* and is slightly decreased in patients with the *CYP2C19*2* or *CYP2C19*3* allele compared with those homozygous for *CYP2C9*1/*1* (45). Tate and collaborators found that the *CYP2C9*3* allele showed significant association with a maximum dose of PHT (46). Taguchi and collaborators evaluated the usefulness of genotyping the CYP2C subfamily in predicting plasma levels and determining the dosage regimens of PHT. Their results showed correlation between the plasma PHT concentrations predicted by genotypes of the CYP2C subfamily and the observed concentrations in some patients. They concluded that the large variability in the clearance of PHT is not completely resolved and that it is important not to overestimate

Table 1 Comparison of the main *CYP2C9* and *CYP2C19* alleles in two populations.

SNP	Amino acid change	Allele[a]	ID dbSNP	Asian, (%)[a] (n=560)	Caucasian, (%) (n=210)
wt	wt	*CYP2C9*1*		0.97	0.74[b]
430C>T	R144C	*CYP2C9*2*	rs1799853	0.00	0.16[b]
1075A>C	I359L	*CYP2C9*3*	rs1057910	0.03	0.10[b]
wt	wt	*CYP2C19*1*		0.72	0.87[c]
681G>A	P227P[d]	*CYP2C19*2*	rs4244285	0.24	0.13[c]
636G>A	W212X	*CYP2C19*3*	rs4986893	0.04	0.0[c]

[a]Mongolian population (30), [b]Spaniards (n=102) (31), [c]European American in Yang et al. (30), [d]aberrant splice site.

the usefulness of genotyping the CYP2C subfamily in determining the dosage of the drug (34).

In light of the present knowledge, it is clear that genotyping of *CYP2C9* and *CYP2C19* could help to identify subjects more prone to show interindividual variability on PHT pharmacokinetics. Therefore, *CYP2C9* and *CYP2C19* genotyping could help to decrease side effects by stratifying drug dosage.

Recently, another allelic variant called *CYP2C9*17* has been reported. This promoter variant is part of the *CYP2C19*17* haplotype, which causes increased activity and increased transcription of *CYP2C19*. Patients carrying this allele might exhibit a lack of response to commonly prescribed dosages of certain proton pump inhibitors and antidepressants due to ultrarapid clearance of these drugs (47–49). It is under consideration for clinical biomarker tests; however, it has not been reported that this allele has any effect in phenytoin or lamotrigine clinical response. Because phenytoin is metabolized via CYP2C19 and CYP2C9, we propose that further studies would be useful to evaluate this allele in terms of PHT response.

UGT and its implication for lamotrigine metabolism

UGT genetic polymorphisms

The UGT enzymes are responsible for the conjugation of glucuronic acid to various endogenous substances and exogenous compounds in a process known as glucuronidation. They are Phase II enzymes that are part of an evolutionary conserved detoxification system, also known as chemical defensome (50). UGTs are localized in the endoplasmic reticulum and use UDP glucuronic acid as a co-substrate for the formation of β-D-glucuronides (51).

UGT-mediated glucuronidation is the most important pathway for the human body's elimination of approximately 35% of all drugs metabolized by Phase II enzymes (52–54). It is also the major pathway for foreign chemical (dietary, environmental, pharmaceutical) removal for most drugs, dietary substances, toxins and endogenous substances (55, 56). Usually glucuronidation results in an inactive hydrophilic compound that inactivates and that can be readily excreted from the body via the urine or the bile (57); although there are some exceptions, such as morphine (58) and retinoic acids (59) that are converted to pharmacologically active glucuronides.

UGTs are membrane bound enzymes localized in the endoplasmic reticulum of liver and extrahepatic tissues. Expression of these enzymes occurs in a tissue-specific manner, with many of the proteins expressed in the liver. However, some enzymes are exclusively expressed in specific extrahepatic tissues, such as the gastrointestinal tract, kidneys, and brain (55, 56, 60).

Genetic variations in specific *UGT* genes have been recognized and can be anticipated for all members of the UGT superfamily. The human UGT superfamily comprises two families (UGT1 and UGT2) based upon sequence relatedness and evolutionary divergence (61, 62). The UGT1 family of proteins is highly conserved in function and has been found in several vertebrates (63–66). The *UGT1A4* locus, located on chromosome 2q37.1, spans approximately 200 kb (67) and encodes at least nine functional UGT1A proteins (UGT1A1 and UGT1A3–10) and three non-functional exon 1 sequences (*UGT1A2*, *UGT1A11*, and *UGT1A12*) (68). Four exons are located at the 3′ end of the *UGT1A* locus, which are combined with one of a consecutively numbered array of first exon cassettes toward the 5′ end of the gene locus to form individual UGT gene products. Therefore, the amino terminal 280 amino acids of UGT1A proteins consists of unique exon 1 encoded sequence and the carboxyl terminal 245 amino acids encoded by exons 2–5 are identical (69, 70). The frequency of genetic variations in *UGT1A4* has been described for Caucasian, Korean and Japanese populations (71–76) (Table 2).

The *UGT1A4* gene is highly polymorphic and according to the UGT alleles nomenclature official page contains 109 SNPs (77). Among them, P24T (70C>A) and L48V (142T>G) exhibit a differential metabolic activity toward mutagenic amines and endogenous steroids, altering hepatic metabolism and detoxification (71, 72). Functional consequences of these SNPs in vitro were an enzyme activity being substrate dependent for P24T and a low activity of the enzyme carrying the L48V substitution (71, 72, 78).

Pharmacogenetics of UGT and LTG: clinical implications

UGT1A4 exhibits catalytic activities mostly for primary and secondary amines that are present in various therapeutic drugs. Among these are a number of psychiatric drugs

Table 2 Comparison of the main *UGT1A4* alleles in three different populations.

SNP	Amino acid change	Allele[a]	Asian, %[b] (n=256)	Caucasian, %[c] (n=100)	Caucasian, %[d] (n=254)
70C>A	P24T	*1A4*2*	0.0[d]	6.0	4.9
			1.0	15.0	20.9
142T>G	L48V	*1A4*3b*	12.9	8.0	8.3
471T>C	C157C	*1A4*1b*	1.0	15.0	20.9

[a](77), [b](73), [c](72), [d](53).

including imipramine, amitriptyline, trifluperazine and LTG (56, 69).

Activity assays of UGT1A4 P24T and L48V showed reduced glucuronidation activities: β-naphthylamine 30% and 50%, and dihydrotestosterone 50% and 0%, respectively (72). A study in Koreans investigating the possible association of UGT1A4 polymorphisms with LTG induced rash found that the L48V c.142T>G polymorphism in the *UGT1A4* gene was not an important factor underlying LTG induced rash development, especially in the absence of P24T polymorphism (75).

It is important to mention that despite the fact that LTG is mainly metabolized by UGT1A4, there are other UGTs such as UGT1A1 and UGT2B7 contributing to LTG glucuronidation (22, 23). The minor contribution of UGT1A1 in LTG glucuronidation has been poorly investigated. One of the common genetic polymorphisms in *UGT1A* genes is a TA insertion in the *UGT1A1* TATA-box; 41 nucleotides upstream of the translation start site, leading to the variant (TA)7 allele (*UGT1A1*28*) instead of the (TA)6 reference allele (*UGT1A1*1*). This *UGT1A1* promoter region dinucleotide repeat polymorphism results in down-regulated levels by altering transcription initiation and also results in an approximately 70% reduction in glucuronidation of bilirubin and other UGT1A1 substrates (79). A number of studies have shown that *UGT1A1*28* is relatively frequent in many populations, with an allele frequency of 32%–39% in Caucasians, 40%–43% in Africans and 16%–18% in Asians (14, 22, 24, 25, 80, 81).

There are few studies analyzing *UGT2B7* gene polymorphisms in epileptic subjects. Several polymorphisms have been identified within the *UGT2B7* gene. The UGT2B7 protein is also found in the brain, kidney, pancreas, mammary gland, lung and gastrointestinal tract, and several additional tissues (80). The A to T transversion at nucleotide 802 leads to a change in amino acid sequence, H268T. This allele is designated as *UGT2B7*2* and their frequency is 48.9% and 26.8% in Caucasians and Asians, respectively (82). Allelic variants have also been identified in the *UGT2B7* promoter that exhibit some dependence on ethnicity haplotype distribution and appear to depend more on linkage to structural variants (82, 83). A haplotype defined by six promoter variants, involving −901G>A and −161T>C, was observed at a frequency between 44% and 55% in Caucasians and approximately 25% in Asians (73).

Although these genetic polymorphisms could alter the efficacy and adverse effects of AEDs, in most cases the functional significance of these SNPs is unclear. This could be due to a number of reasons: isozyme substrate specificity remains poorly defined, isoforms might exhibit overlapping substrate specificity or the domains of UGT proteins responsible for substrate binding are not identified (14, 24, 84). Moreover the UGT isozymes involved in the metabolism of each anticonvulsant are not yet well defined and some anticonvulsants can be metabolized by more than one isozyme (25).

Recently, Sánchez and collaborators analyzed the polymorphisms UGT2B7 161C>T and UGT2B7 372A>G and their contribution to the interindividual variability in LTG concentration to dose ratio (LTG-CDR) in epileptic patients. A significant association was found between LTG-CDR and UGT2B7 −161C>T polymorphism, when patient age and concomitant AEDs were taken into account in a multivariate analysis (24).

Conclusions and perspectives

In spite of all the studies on the pharmacogenetics of AEDs, the application of pharmacogenetic knowledge to clinical routine is limited in current practice.

To promote the application of pharmacogenetic knowledge in clinical routine, research on genotype based dose adjustments is still necessary, as is the promotion of faster and cheaper genotype analyses. Furthermore, the benefits of performing DNA genotyping to predict drug response and side effects should be evaluated in properly designed prospective pharmacogenetics trials.

For the use of PHT, the relevance of *CYP2C9* and *CYP2C19* must be also specifically considered, as well as for the use of LTG the relevance of *UGT1A4* and *UGT2B7* genetic polymorphisms.

In the near future, genetic factors should be considered when an antiepileptic drug is prescribed. Thus, personalized medicine could be of use for the treatment of epilepsy and help in achieving the dream of selecting the right drugs for the right patient at the right dosage. Although present information is not enough to fully personalize the treatment of epilepsy, there is sufficient available evidence to identify genetic risk factors related to lack of response or side effects. Therefore "stratified" medicine can be applied for improving the pharmacological treatment of epilepsy.

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Conflict of interest statement

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