Effect of CYP2C9/CYP2C19 polymorphism on pharmacokinetics of phenobarbital in Korean neonatal seizure patients

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ABSTRACT

Effects of cytochrome P450 (CYP) 2C9/2C19 polymorphisms

on pharmacokinetics of phenobarbital

in neonates and infants with seizures

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(Directed by Professor Chul Lee)

Phenobarbital, commonly used as the preferred treatment for neonatal seizure, is a drug that requires careful dose adjustments based on therapeutic drug monitoring. It has been reported that phenobarbital metabolism was affected by cytochrome P450 (CYP) 2C9/2C19 polymorphisms in adults requiring dose adjustment. The aim of the study was to evaluate the effects of CYP 2C9/2C19 genetic polymorphisms on

phenobarbital pharmacokinetics (PK) in neonates and infants with seizures.

CYP2C9/CYP2C19 (homozygous extensive metabolizer; wild type: CYP2C91*1/*1, CYP2C19*1/*1, heterozygous extensive metabolizer: CYP2C19*1/*2, *1/*3 and poor metabolizer: CYP2C9*1/*3, CYP2C19*2/*2, *2/*3) genetic polymorphisms in 52 neonates and infants with seizures, who were hospitalized for treatment at Gangnam Severance Hospital and Severance Children's Hospital, were analyzed. PK parameters were compared based on genotypes. The NONMEM program was used for population PK modeling. No significant differences in phenobarbital clearance (CL), volume of distribution (Vd) and concentrations were shown among the CYP2C9/2C19 genotype groups. The results of PK modeling were as follows: $Vd=3590 * (\text{body weight (BWT)}/4)^{0.766} * (\text{AGE}/2)^{0.283}$ and $CL=32.6*(\text{BWT}/4)^{1.21}$.

Phenobarbital PK parameters of neonates and infants with seizures were not significantly different among the groups with different CYP2C9/CYP2C19 genotypes. The addition of CYP2C9/CYP2C19 genotypes to PK models did not improve the dosing strategies in neonates and infants.

Key words: Cytochrome p-450 enzyme system, CYP2C9, CYP2C19, genetic polymorphism, phenobarbital, neonatal seizure

Effects of cytochrome P450 (CYP) 2C9/2C19 polymorphisms

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I. INTRODUCTION

Genetic polymorphisms of cytochrome P450 (CYP) enzymes mainly influence drug metabolism, disposition, and elimination and lead to alteration of pharmacokinetic (PK) parameters resulting in changes in drug exposure and response, and frequently and consequently associated with adverse drug reactions profiles or treatment failures [1,2]. Changes in drug exposure caused by CYP polymorphisms could be overcome by drug dosage adjustment, if appropriately estimated [3]. Phenobarbital is eliminated by CYP450 2C9- and/or 2C19-dependent oxidation (25%) and N-glucoside formation (25%) and renal excretion (25%) [4,5]. In fact, CYP 2C9/2C19 genetic polymorphisms

have been shown to influence the clearance of phenobarbital in adult patients requiring dose adjustment [6 7]. However, because of the developmental ontogeny of hepatic metabolizing enzymes, the enzyme expression patterns and activities and consequently the PK profiles of neonates and infants are quite different from those of adults [8-15]. Further investigation into the PK profiles of neonates and infants with regard to genetic polymorphisms of relevant hepatic enzymes is warranted.

In this study, the aim was to evaluate the effects of the CYP 2C9/2C19 genetic polymorphisms on phenobarbital PK profiles in neonates and infants with seizures, and to devise an optimal dosing strategy using the population PK modeling methods.

II. PATIENTS AND METHODS

1. Patients

The clinical study protocol was approved by the IRBs. In the study, 52 neonates and infants who were diagnosed with seizures were enrolled. The patients were admitted to the NICUs of Severance Children's Hospital and Gangnam Severance Hospital between December 2007 and December 2009 and received phenobarbital monotherapy for the control of seizures. Eight patients were excluded due to inappropriate blood collections for PK analysis either before reaching the steady state or before 7 days of age, the period when drug metabolism is known to be unstable. Among the 44 infants, 27 male and 17 female infants showed an age range of 8 days

to 6 months and body weight range of 2.1 to 8.0 kg. Due to the wide range of age and body weight, the patients were stratified into two groups based on their ages to control for the age and body weight (Group 1: between 8 days and 3 months; Group 2: between 4 and 6 months) for subgroup analysis. Infants with severe structural anomaly in central nervous system, severe systemic illnesses, hepatic or renal failure, congenital hemolytic anemia, or genetic disorders were excluded.

All infants were given one loading dose of 20 mg/kg phenobarbital IV, followed by maintenance doses of 2.5 mg/kg every 12 h. If seizure was uncontrollable, multiple loading doses of 10 mg/kg phenobarbital IV were added. A total of 115 trough serum concentrations (1 to 4 samples per patient) were obtained: first measurements usually at 48 hrs (range 35 – 59 hr) and the next at 11.5 days (range 8-19 days) from the initiation of therapy. The drug concentrations were measured using a fluorescence-polarization immunoassay method (Abbott TDx analyzer). TDM Analysis was done by the Abbott based PK software Program. All infants were classified into homozygous extensive metabolizers (EMs) for the wild type, heterozygous EMs, and poor metabolizers (PMs) by genotyping.

2. CYP 2C9/2C19 Genotyping

For genotyping procedures for CYP2C19 and CYP2C9 blood samples (1 mL) were obtained from all patients, and genomic DNA was isolated from peripheral

lymphocytes using an extraction kit (GENOMIX, Talent, Italy). CYP2C9 polymorphism (430C>T(C144R), rs1799853) & CYP2C19 polymorphism (991A>G(I331V), rs3758581) were screened using single base primer extension assay using ABI PRISM SNaPShot Multiplex kit (ABI, Foster City, CA, USA) according to the manufacturer's recommendation. Briefly, the genomic DNA flanking the SNP (C144R rs1799853) was amplified with PCR reaction with 5'-AGATGGAAAACAGAGACTT-3' (Forward) and 5'-AGCTAACAACCAGGACTCA-3' (Reverse) primer pairs, and the genomic DNA flanking the SNP (I331V, rs3758581) was amplified with PCR reaction with 5'-CAGGAAACAGCTATGACCtgcctagcttaaggcaca-3' (Forward) and 5'-TGTAAAACGACGGCCAGTcccaaactggaatcaaca-3' (Reverse) primer pairs.

Standard PCR reagents in 10 microliter reaction volume, containing 10 ng of genomic DNA, 0.5 pM of each oligonucleotide primer, 1 microliter of 10X PCR Gold buffer, 250 M dNTP, 3 mM $MgCl_2$ and 0.25 unit i-StarTaq DNA Polymerase (iNtRON Biotechnology, Sungnam, Kyungki-Do, Korea). The PCR reactions were carried out as follows: 10 minutes at 95℃ for 1 cycle, and 30 cycles on 95℃ for 30s, 60℃ for 1 minute, 72℃ for 1 minute followed by 1 cycle of 72℃ for 7 minutes. After amplification, the PCR products were treated with 1 unit each of shrimp alkaline phosphatase (SAP) (Roche) and exonuclease I (USB Corporation) at 37℃ for 60 minutes and 72℃ for 15 minutes to purify the amplified products. One microliter of

the purified amplification products were added to a SNaPshot Multiplex Ready reaction mixture containing 0.15 pmol of genotyping primer (5'-GGGCTTCCTCTTGAAACAC -3'and 5'- GCAGGGGCTCCGGTTTCTGCCAA -3') for primer extension reaction. The primer extension reaction was carried out for 25 cycles of 96℃ for 10 seconds, 50℃ for 5 seconds, and 60℃ for 30 seconds. The reaction products were treated with 1 unit of SAP at 37℃ for 1 hour and 72℃ 15 minutes to remove excess fluorescent dye terminators. One microliter of the final reaction samples containing the extension products were added to 9 microliter of Hi-Di formamide (ABI, Foster City, CA). The mixture was incubated at 95℃ for 5 minutes, followed by 5 minutes on ice and then analyzed by electrophoresis in ABI Prism 3730xl DNA analyzer. Results were analyzed using GeneScan analysis software (ABI, Foster City, CA).

CYP2C9 (-1188T>C, rs4918758 and 1075A>C(I359L), rs1057910) and CYP2C19 polymorphisms (G681A(P227P), rs4244285 and 636G>A(W212X), rs4986893), were screened using the TaqMan fluorogenic 5' nuclease assay (ABI, Foster City, CA, USA). The final volume of polymerase chain reaction (PCR) was 5 μL, containing 10 ng of genomic DNA and 2.5 μL TaqMan Universal PCR Master Mix, with 0.13 μL of 40X Assay Mix (Assay ID C___1329192_10, C__27104892_10 for CYP2C9 and C__25986767_70, C__27861809_10 for CYP2C19). Thermal cycle conditions were as follows: 50℃ for 2 min to activate the uracil N-glycosylase and to prevent carry-

over contamination, 95℃ for 10 min to activate the DNA polymerase, followed by 45 cycles of 95℃ for 15 s and 60℃ for 1 min.

All PCR were performed using 384-well plates by a Dual 384-Well GeneAmp PCR System 9700 (ABI, Foster City, CA, USA) and the endpoint fluorescent readings were performed on an ABI PRISM 7900 HT Sequence Detection System (ABI, Foster City, CA, USA). Duplicate samples and negative controls were included to ensure accuracy of genotyping.

3. Population Pharmacokinetic Model Development

Population PK modeling was carried out using the nonlinear mixed-effects software in NONMEM®, version 6.2 (ICON, Ellicott City, USA) [16]. An one-compartment intravenous administration model with first-order elimination was used.

C_{ij} (ug/ml) = $D * e^{-(CL_i/V_i)t_{ij}/V_i}$

C: serum concentration (mcg/mL) , D: dose per body weight (mg/kg), CL: total body clearance per body weight (ml/kg/h), V: Volume of distribution (L/Kg)

Model 1: $CL_i = \theta 1$, $V_i = \theta 2$

Model 2: $CL_i = \theta 1 * BWT_i$, $V_i = \theta 2 * BWT_i$

Model 3 : $CL_i = \theta 1 * BWT_i * age_i$, $V_i = \theta 2 * BWT_i * age_i$

Model 4 : $CL_i = \theta 1 * BWT_i * age_i * GT_i$, $V_i = \theta 2 * BWT_i * age_i * GT_i$

GT = parameter for genotyping .

Inter-patient variability in the CL : $CLi = Cli(1+\eta_i)$

Cli: ith CL predicted for the $_i$ th patient with the regression model

η_i: independently distributed random variable with mean zero and variances

The body weight (BWT), age, gender, genotypes of CYP2C19, and laboratory findings (AST, ALT, protein, albumin, BUN, and creatinine) were screened as covariates to test the significant influence on clearance (CL) or volume of distribution (Vd). To test the significance of various factors that influence CLij, we used the value of objective function (OBJ) determined in the NONMEM setting.

4. Statistical analyses

One-way ANOVA for multiple group comparisons was done with SPSS software version 17.0 (SPSS, Chicago, IL). P-values less than 0.05 were considered statistically significant.

III. RESULTS

The data from 52 Korean neonates and infants with seizures, with a total of 115 serum concentrations of phenobarbital, were included in the population pharmacokinetic study. The patient characteristics by the genotype CYP2C19 and CYP2C9 are shown in table 1 and 4. Twenty three patients (52%) had no mutations in

the CYP2C19 gene (CYP2C19*1/*1), while 13 patients (30%) were heterozygous for the CYP2C19 mutation (*1/*2 or *1/*3) and 8 patients (18%) were PM of CYP2C19 (*2/*2, *2/*3). Forty one patients (94.2%) had no mutations in the CYP2C9 gene (CYP2C9*1/*1), while 3 patients (5.7%) were PM of CYP2C9 (*1/*3). No significant differences were seen in the sex, age, body weight, dose of phenobarbital administered, or concentration of phenobarbital among the genotype groups.

In both age groups, there were no statistically significant differences in the steady state phenobarbital concentrations, CL and Vd based on CYP2C19 genotype (Tables 2 and 3, Figure 1). However, when the two age groups were compared, we found higher phenobarbital concentrations and lower CL in Group 1. A wide inter-individual variation in the plasma concentrations among the genotype groups was noted although it was not statistically significant. The mean values of CL and Vd in CYP2C19 PM patients were lower than those in wild type of CYP2C19, but with no statistically meaningful differences. Renal function, as determined by plasma creatinine concentrations, and liver function were normal in all infants. Statistical comparison of biochemical lab parameters among genotype groups showed no difference. The pharmacokinetic data of the CYP2C9 genotype groups are shown in Table 5. There was no effect of CYP2C9 polymorphism on the pharmacokinetic profiles of the genotype groups. The serum concentrations of all the infants at the second measurement were within the steady state therapeutic concentration ranges (15-40

μg/mL).

Table 1 Demographics and treatments by CYP2C19 genotype

	Wild type (*1/*1)	EMs (*1/*2, *1/*3)	PMs(*2/*2, *2/*3)
Number of patients	23 (52%)	13 (30%)	8 (18%)
Group 1 (n)	17	10	4
Group 2 (n)	6	3	4
Male/Female	13/10	8/5	4/4
Age (months) †	2.4 ± 1.9	1.4 ± 1.6	3.3 ± 2.5
Group 1	1.6 ± 1.4	0.8 ± 0.3	0.6 ± 0.3
Group 2	5.2 ± 0.8	5.0 ± 1.7	5.3 ± 0.9
Weight (kg) †	5.0 ± 2.7	5.3 ± 4.3	6.4 ± 3.1
Group 1	4.1 ± 2.1	5.1 ± 4.7	4.1 ± 3.3
Group 2	8.3 ± 2.7	7.8 ± 2.4	7.5 ± 1.1
Phenobarbital loading dose (mg/kg/d) †	25.6 ± 4.6	23.1 ± 3.4	26.7 ± 2.8

Phenobarbital daily dose (mg/kg/d) †	5.1 ± 0.5	5.0 ± 0.3	5.1 ± 0.4

† mean ± SD,

Group 1; age between 8 days and 3 months, Group 2; age between 4 and 6 months.

Demographics and treatments were not significantly different among CYP2C19 genotype groups ($p > 0.05$).

Table 2 Pharamacokinetic profiles by CYP2C19 genotype in Group 1 (age between 8 days and 3 months).

	Wild type (*1/*1)	EMs (*1/*2, *1/*3)	PMs (*2/*2, *2/*3)	P value
Number of patients	17	10	4	
Phenobarbital concentration. (ug/mL) †	29.6 (17.0-38.2)	27.8 (19.9-61.8)	24.8 (20.3-33.7)	0.614
Vd (L/kg) †	0.85 (0.58-1.1)	0.92 (0.47-1.34)	0.60 (0.60-0.99)	0.235
CL (mL/kg/h) †	6.5 (4.2-13.1)	6.6 (5.1-9.9)	7.0 (4.4-7.9)	0.761

† median (range).

Vd: Volume of distribution, CL: clearance

Table 3 Pharamacokinetic profiles by CYP2C19 genotype in Group 2 (age between 4 and 6 months).

	Wild type (*1/*1)	EMs (*1/*2, *1/*3)	PMs (*2/*2, *2/*3)	P value
Number of patients	6	3	4	
Phenobarbital concentration. (ug/mL) †	22.3 (15.3-26.7)	16.4 (12.7-29.7)	14.0 (9.1-22.2)	0.271
Vd (L/kg) †	0.60 (0.44-0.90)	0.60 (0.60-0.92)	5.30 (5.13-15.71)	0.695
CL (mL/kg/h) †	9.3 (7.4-11.7)	5.3 (5.1-15.7)	14.3 (10.2-18.3)	0.811

† median (range).

Vd: Volume of distribution, CL: clearance

Table 4 Demographics, treatments, and PK profiles by CYP2C9 genotype

	Wild type (*1/*1)	PMs (*1/*3)
Number of patients	41 (93.2%)	3 (6.7%)
Male/Female	21/20	2/1
Age (months) †	2.1 ± 1.5	4.2 ± 1.5
Weight (kg)†	4.8 ± 0.9	7.2 ± 1.6
Phenobarbital loading dose (mg/kg/d)†	22.6 ± 4.6	24.1 ± 3.4
Phenobarbital daily dose (mg/kg/d)†	5.1 ± 0.3	5.0 ± 0.2
Phenobarbital concentration (ug/mL)†	23.7 ± 9.1	18.8 ± 4.5
Vd (L/kg)†	0.78 ± 0.29	0.85 ± 0.15
CL (ml/kg/h)†	6.4 ± 4.6	6.8 ± 1.7

† mean ± SD.

No significant differences between CYP2C9 genotype groups ($p > 0.05$).

Vd: Volume of distribution, CL: clearance,

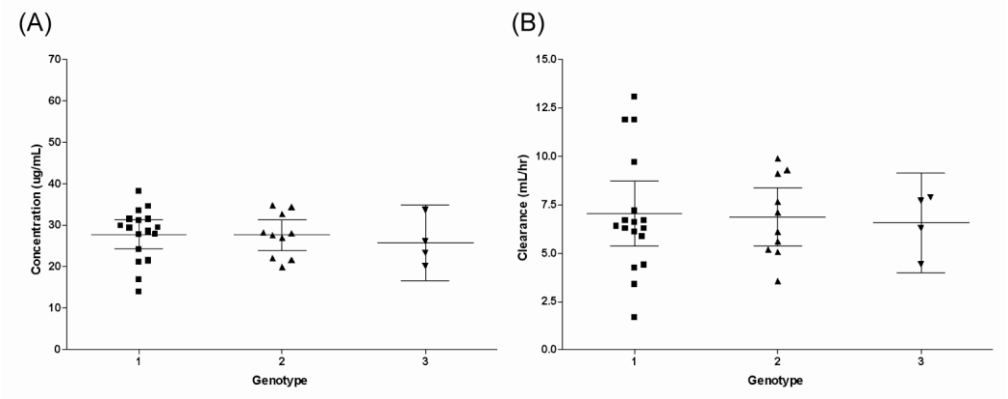

Figure 1 (A) Scatter plot of the individual concentration of phenobarbital grouped by cytochrome P450 (CYP) 2C19 genotypes. (B) Scatter plot of the individual clearance of phenobarbital grouped by CYP2C19 genotypes. 1=wild type extensive metabolizer (EM) (*1/*1), 2=heterozygous EM (*1/*2,*1/*3), 3=poor metabolizers (PM) (*2/*2, *2/*3). The horizontal lines represent the median and 95% CI.

NONMEM was used to evaluate and to model mathematical relationships between the values of CL and V versus a variety of covariates including genotype. The results of the NONMEM analysis are summarized in Table 5 and Figure 2. Population mean parameters and their variances were obtained. First, in the process of model developing, each covariate was added one by one to the CL and V model. Potentially significant variables were included in the full covariate model for CL. CYP2C9/2C19 genotypes and laboratory findings (AST, ALT, BUN, Cr, protein, albumin) did not show a significant influence on CL or V by the backward elimination method, and

they were removed from the full model. Influence of BWT on CL and Vd as well as that of age on Vd was significant after both forward selection and backward elimination. A proportional error model best described the inter-individual variability, whereas an additive error model was the most satisfactory for any residual error. The final model was as follows:

Typical value of Vd (mL) = $3590 * (BWT/4)^{0.766} * (AGE/2)^{0.283}$

Coefficient of variation of Vd = 31.1%

Typical value of CL (mL/h) = $32.6 * (BWT/4)^{1.21}$

Coefficient of variation of CL = 27.0%

No significant effects of CYP2C genotypes were found on the phenobarbital pharmacokinetics in the groups of neonates and infants with seizures.

Table 5 Phenobarbital population pharmacokinetic modeling

Model		Obj	Parameters	Thetas	Etas	Eps
PB0	Basic model	557.865	7	4	2	0
PB1	BWT on V	545.858	8	5	2	0
PB2	+ AGE on V	540.217	9	6	2	0
PB3	+ BWT on CL	505.428	10	7	2	0
PB4	+ AGE on CL	504.038	11	8	2	0

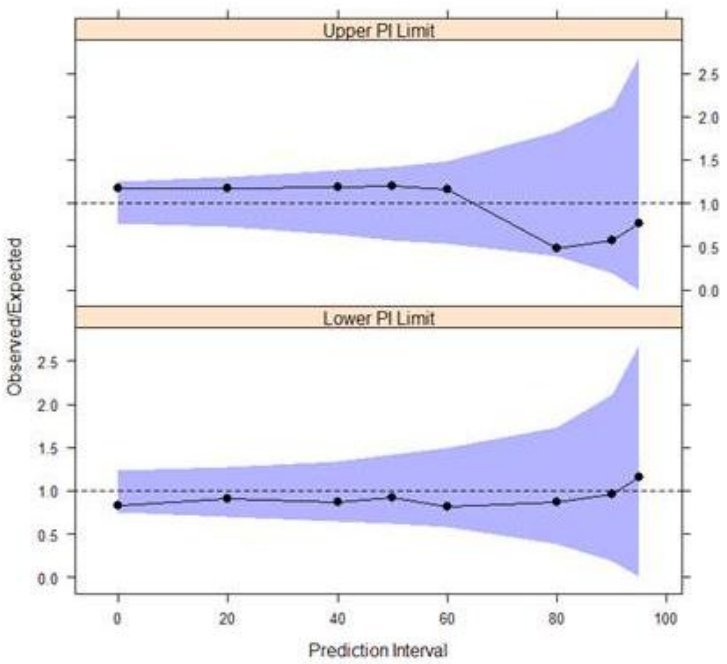

Figure 2 Numerical Predictive Check for the final model. Lines with solid circles: The ratios of the observed to the expected values of the overall number of observations outside the different prediction intervals. Shaded area: Expected 95% confidence intervals for the number of observations outside each PI calculated based on the simulated datasets.

IV. DISCUSSION

The effects of CYP2C9/2C19 polymorphisms on the phenobarbital exposure due to changes in phenobarbital pharmacokinetic profiles in neonates and infants have not previously been evaluated or reported. In the present study, the CYP2C9/2C19 genetic polymorphisms of neonates and infants with seizures were characterized, and the PK parameters were compared based on the genetic profiles. Unlike in adults [6 7], the effects of genetic polymorphisms of CYP2C9/2C19 on the phenobarbital pharmacokinetics were not significant in infants. Population PK modeling showed that CYP2C9/2C19 as a covariate did not improve the PK models but confirmed that body weight was the most important covariate for CL and age and body weight for Vd.

Drug response is largely influenced by individual genetic factors. Pharmacogenetics seeks to optimize drug treatment by tailoring drug selection and drug dosage to the patient's genetic make-up. Drug treatment is more efficacious if the patient gets individually optimized doses of only those medicines to which he/she responds[1]. It is

also safer because some side-effects can be avoided.

Phenobarbital requires therapeutic drug monitoring for efficacy and toxicity. It is eliminated in part through metabolism such as aromatic hydroxylation to form p-hydroxyphenobarbitone by CYP isoenzymes (25%) and N-glucosidation to form phenobarbitone glucoside (25%) or excreted unchanged in urine (25%)[4]. In general, the half-life of phenobarbital varies with age from 114.2 ± 40.3 h during the early neonatal period to 41.2 ± 13.9 h after 1 month of age [5 17-20]. Clearance is also variable between 0.0053 and 0.0141 L/kg/h during the early period and increases with age[5 19 20]. The results of the study showed the mean clearance of 0.0084 L/kg/h and Vd of 0.9 L/kg, which are compatible with the published results.

The allele frequency of CYP2C9*3 is noted to be relatively rare in Korea[10], and CYP2C9*2 appears to be absent in East Asians[11]. The allele frequency of CYP2C9*3 in Korean is 0.057, a value higher than in Japanese (0.021) and considerably lower than in Caucasians (0.085).[12] None of the infants in the present study were found to have CYP2C9*2 genotype.

In a report on the effects of CYP2C19 polymorphism on phenobarbital pharmacokinetics in Japanese adult patients, the total CL of phenobarbital significantly decreased by 18.8% in CYP2C19 PMs relative to that in EMs [7]. Another report showed significant effects of CYP2C9 polymorphism on phenobarbital CL, where the total clearance of phenobarbital decreased by 48% in CYP2C9 PM patients

in comparison with those with wild type ($p< 0.001$) [6]. In the present study, CL and Vd of infants who were CYP2C9 and CYP2C19 PM were not significantly different from either wild type or heterogeneous EM groups. This lack of difference may be due to the CYP450 isoform-specific developmental status in neonates and young infants[11]. CYP2C19 expression at the mRNA level reaches the adult level soon after birth. However, the protein level of infants increases slowly and takes five years to reach the adult level [8]. The enzyme activity in infants is approximately 30% of that in adults, which is achieved by 1 year of age [12-14]. The total CYP contents in the liver are relatively constant until 1 year of age, remaining 30 % to 60% of the adult level [21]. Because of the relatively low metabolic enzyme activities of the wild types during early infancy, the differences in enzyme activities between wild types and poor metabolizers would not be as prominent as seen in adults.

Some discrepancies exist between the reported phenobarbital PK models in adults. Mamiya et al. studied 74 adults (ranging 17-76 yr) and showed CYP2C19 PM (*2/*2, *2/*3) to have significant effects on CL in their model [7]. On the other hand, Goto et al. showed that body weight and CYP2C9PM (*1/*3) had influence on the CL, but not on CYP2C19 PM, where the population studied included both pediatric and adult patients with a mean age 13.72 years (ranging 0.8 - 43.8 year) [6]. In the present study, the model for CL showed that CL was mainly influenced and predicted by a function of body weight, while the model for Vd was a function of body weight and age. CYP2C19

genotype status added as a covariate did not improve the models.

Since valproic acid is reported to inhibit both the p-hydroxylation and N-glucosidation of phenobarbital, it significantly reduces phenobarbital metabolism and total CL.[8] Phenytoin is also shown to have a significant interaction with phenobarbital.[9] In order to exclude the effect of other drugs on the pharmacokinetics of phenobarbital, we selected only those patients who were treated with phenobarbital alone.

There are some limitations in the study: a small number of patients, stratification of the study participants into different age groups that further decreased the number of patients in each group, and limited genotyping (CYP2C9*1/*3 and 2C19*1,*2,*3 only).

V. Conclusion

This is the first study to analyze the effects of CYP2C9/2C19 polymorphisms on the pharmacokinetics of phenobarbital in neonates and infants with seizures. Unlike in adults, CYP2C9/2C19 poor metabolizers in these age groups did not have a significant influence on the PK profiles of phenobarbital. Addition of CYP2C9/2C19 genotype as a covariate in the pharmacokinetic modeling of CL and Vd would not improve the personalized optimal drug dosing strategy for phenobarbital therapy for neonates or infants with seizures.

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ABSTRACT (IN KOREAN)

경련을 보인 한국인 신생아와 영아 환아에서 CYP2C9/2C19 다형성성이 페노바비탈 약동학에 미치는 영향에 관한 연구

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목적: 페노바비탈은 전세계적으로 사용되는 항전간제로서, 적정 치료 용량의 결정을 위해 총 체내 청소율에 영향을 미치는 인자 중 약물 유전학적인 인자로서 CYP2C9/2C19 유전적 다형성이 성인에서 약물용량에 영향을 미친다고 알려져 있다. 이에 경련을 보인 신생아 및 영아 환아에서 CYP2C9/2C19 의 다형성을 확인하여 페노바비탈 약동학에 미치는 영향을 규명하여 치료에 도움이 되고자 한다

방법: 연세대학교 의과대학 세브란스병원과 강남세브란스병원에 내원하여 신생아 경련을 진단 받고 페노바비탈을 투여 받은 본 연구에 동의한 환자 52 명을 대상으로 한다. CYP2C9/CYP2C19 (homozygous extensive

metabolizer; wild type: CYP2C1*1/*1, CYP2C19*1/*1, heterozygous extensive metabolisers: CYP2C19*1/*2, *1/*3 and poor metabolizer: CYP2C9*1/*3, CYP2C19*2/*2, *2/*3) 유전자 다형성성을 확인하고 이에 따른 약동학적 인자와 비교 분석을 시행하고 집단약동학적 분석을 시행하였다.

결과: CYP2C9/2C19 유전자 다형성성은 페노바비탈 약동학에 유의한 영향을 미치지 않았다. NONMEM을 이용한 모델링 결과는 다음과 같다.

$Vd=3590 * (\text{body weight (BWT)}/4)^{0.766} * (AGE/2)^{0.283}$

$CL=32.6*(BWT/4)^{1.21}$.

결론: 본 연구는 경련을 보인 신생아와 영아에서 CYP2C9/2C19 유전적 다형성이 페노바비탈의 약동학에 유의한 영향을 미치지 않는 것을 확인하였다. 신생아와 영아 시기에는 페노바비탈의 유전자 다형성성을 약동학 모델에 추가하는 것은 페노바비탈 약물용량 결정에 유용하지 않다고 생각된다.

핵심되는 말: 신생아 경련, 페노바비탈, 유전적 다형성성, CYP 450 효소 체계, CYP2C19, CYP2C9