CHARPTER I
INTRODUCTION

Background and Rationale

Carbamazepine (CBZ) is a first-line antiepileptic drug for partial and generalized tonic–clonic seizures.[1-5] CBZ is used as monotherapy or coadministration with other antiepileptic drugs (AED) such as Phenytoin (PHT), Phenobarbital (PB), Valproic acid (VPA).[5-7] Additionally, it is commonly used for others neurological disease for instance pain relief in trigeminal neuralgia, bipolar disorder. [8] CBZ is metabolized 99% by the liver; *CYP3A4* and *CYP3A5* are the most importance enzymes. [8-11] The serum concentration of CBZ that reported to be the accepted therapeutic range is 4-12 mg/L when the drug is used for the treatment of seizures, however, the range for psychiatric disorders and trigeminal neuralgia is assumed to be the same. [9]

Studies about the clearance of CBZ are importance for therapeutic drug monitoring. Several studies reported that age, body weight, surface area, dose of CBZ, dose of PB, and co-medication with PHT, PB, or VPA are significant influence on CBZ clearance. [8, 9, 12-14] Recent pharmacogenomic studies found that *CYP3A5* polymorphism effects on CBZ clearance. Seo et al. [15] reported that CBZ clearance in patients with *CYP3A5*3/*3* was 8% higher than in patients with *CYP3A5*1/*1* and *CYP3A5*1/*3*. Park et al. [16] reported that the mean of level-to-dose-ratio of CBZ in patients with *CYP3A5*3/*3* was 31% significant higher than patients with *CYP3A5*1/*1* and *CYP3A5*1/*3* ($p = 0.032$), and the CBZ clearance was 29% significant lower ($p = 0.004$). Studies about the effect of *CYP3A5*3* on CBZ pharmacokinetics when comedication with other AEDs that reported to have pharmacokinetic interaction with CBZ have not been clearly defined. In Thailand there has never been study about the effect of *CYP3A5* polymorphism on CBZ clearance either in patients with CBZ monotherapy or coadministration with other AEDs which have drug interaction, such as, PHT, PB and VPA. Knowledge about the effect of *CYP3A5* polymorphism on CBZ pharmacokinetics may be useful in therapeutic plans to avoid serum drug concentration-related adverse

effects and reduce inappropriate dosage. A recent study reported that the frequency of *CYP3A5*3* allele in a Thai population was 66%. [17]

CBZ is mainly metabolized by the liver via CYP450, the same enzyme system as PHT and PB, at the same time, CBZ induces uridine diphosphate glucuronosyltransferase (UDPGT) which is the main metabolizing enzyme of VPA while VPA inhibits CBZ-10, 11-epoxide (active metabolite) metabolism via Epoxide hydrolase [6-9]. It is therefore highly possible that CBZ pharmacokinetic parameters could be related to pharmacokinetic parameters of PHT, PB and VPA. In Thailand the relationship between pharmacokinetic parameters of PHT and CBZ has been investigated and found that there was high correlation between clearance of CBZ and maximum rate of metabolism of PHT (PHT V_{max}) (correlation coefficient = 0.828), regression equations to predict CBZ clearance from PHT V_{max} or vice versa have also been provided [18], even though validation and application has never been performed. Additionally, the study of correlation between CBZ clearance and PB clearance and VPA clearance has never been investigated.

The purpose of this study was to determine the effect of *CYP3A5* polymorphism on CBZ clearance, provide the regression equation to predict CBZ clearance from demographic data and polymorphism of *CYP3A5* and investigate the correlation between CBZ clearance and PHT V_{max}, PB clearance or VPA clearance and develop regression equation to predict CBZ clearance from clearance of other AEDs or vice versa. The ultimate goal is to provide a more accurate and simplified method for predicting the appropriate dosage of CBZ and in turn, a higher efficiency and safety of drug used.

Hypothesis

1. CBZ clearance was not different between patients with *CYP3A5*1* and *CYP3A5*3* alleles.
2. CBZ clearance was not correlated with PHT V_{max}, PB clearance or VPA clearance.

Objective

1. To compare clearance, level-to-dose-ratio of CBZ between patients with *CYP3A5*1* and *CYP3A5*3* either when CBZ was used as monotherapy or coadministration with PHT, PB or VPA.
2. To provide regression equation to predict CBZ clearance from demographic data and polymorphism of *CYP3A5*.
3. To determine relationship between CBZ clearance and PHT V_{max}, PB clearance and VPA clearance.

Significant of the study

1. Information about the difference between CBZ clearance in patients with *CYP3A5*1* VS *CYP3A5*3* may be useful for the dosage regimen plans.
2. Information about the factors that correlate with CBZ clearance may be used to therapeutic plans to avoid serum drug concentration-related adverse effects and add efficiency to drug used.
3. To provide equation to predict CBZ clearance, and in turn, to predict a more appropriate dosage regimen for the patient.

Scope of this study

1. Populations of this study are the outpatients at Prasat Neurological Institute who used CBZ as monotherapy or coadministration with PHT, PB or VPA.
2. Variables of this study: Dependent variables are CBZ clearance, CBZ level-to-dose-ratio. Independent variables are *CYP3A5* polymorphism, PHT V_{max}, PB clearance, VPA clearance and demographic data.

Limitation of this study

Application of this study is limit to specific patients that have the same characteristics as the patients in this study.

Conceptual framework

Conceptual framework is shown in figure 1.

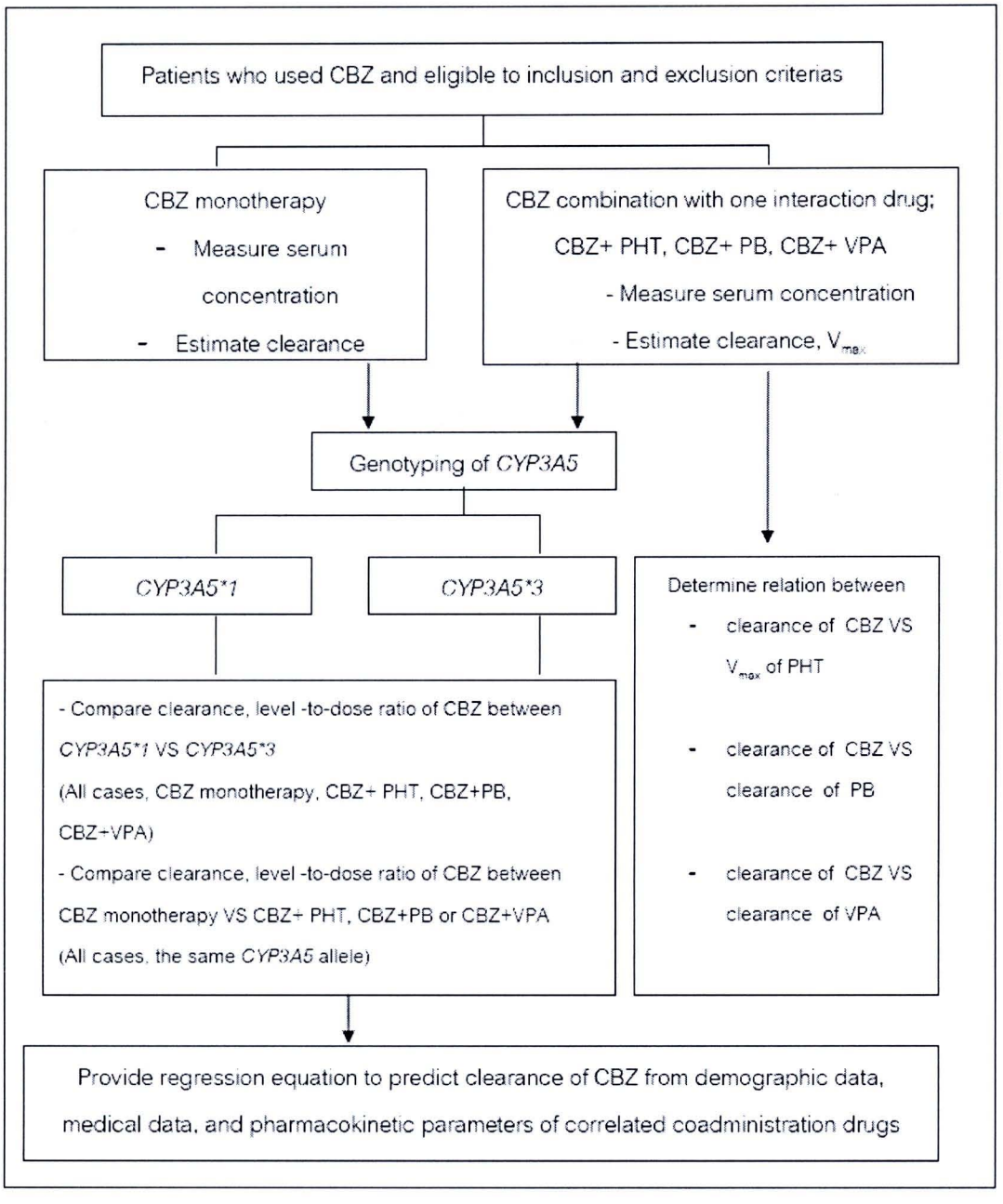

Figure1: Conceptual framework

Operational definition

1. *CYP3A5* polymorphism is genotype that control *CYP3A5* enzyme producing which has single-nucleotide polymorphism; *CYP3A5*3* allele is substitute amino acid at intron 3 (6986 A>G) when the reference allele is *CYP3A5*1*.
2. Antiepileptic drugs serum concentration measurement is a measurement of bound and unbound drug in serum (total drug) that the sampling time is not over one hour before the administration of the next dose in the morning (trough level).
3. Clearance is the ability of the body or organ (liver, kidney) to eliminate a drug. This pharmacokinetic parameter is calculated from serum concentration level at steady state.
4. Level-to-dose ratio is a ratio of antiepileptic drug serum level to dose per day of the drug.