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DRUG INTERACTIONS MONITORING IN EPILEPTIC CLINIC AT NEUROLOGICAL INSTITUTE

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เสริมสุข จันทร์ใต้ : การติดตามการเกิดอันตรกิริยาต่อกันระหว่างยาในคลินิกโรคลมชัก สถาบันประสาทวิทยา (DRUG INTERACTION MONITORING IN EPILEPTIC CLINIC AT NEUROLOGIACAL INSTITUTE) อาจารย์ที่ปรึกษา : ดร. พรอนงค์ อร่ามวิทย์ อาจารย์ที่ปรึกษาร่วม : รศ. ดร. จุฑามณี สุทธิสีสังข์

การศึกษานี้เป็นการศึกษาแบบพรรณนาไปข้างหน้า ในคลินิกโรคลมชักของสถาบันประสาทวิทยาในช่วงระยะเวลา 10 เดือน ตั้งแต่วันที่ 1 มิถุนายน พ.ศ.2545 ถึง 31 มีนาคม พ.ศ. 2546 โดยมีวัตถุประสงค์เพื่อหาความชุกของการเกิดอันตรกิริยาต่อกันระหว่างยากันชัก และยากันชักกับยาอื่น และเปรียบเทียบคุณภาพชีวิตของผู้ป่วยก่อนและหลังการติดตามโดยเภสัชกร การติดตามการเกิดอันตรกิริยาต่อกันระหว่างยาในผู้ป่วยจะทำการติดตามอย่างน้อย 1 ครั้งซึ่งมีระยะเวลาห่างกันอย่างน้อย 1 เดือนแต่ไม่เกิน 3 เดือน ผลการเก็บข้อมูลผู้ป่วยทั้งสิ้นจำนวน312 คน พบความชุกของการเกิดอันตรกิริยาต่อกันระหว่างยาทั้งหมดคิดเป็นร้อยละ 27.88 (87 ราย) แยกเป็นการเกิดอันตรกิริยาต่อกันระหว่างยาที่อาจเป็นไปได้คิดเป็นร้อยละ 26.28 (82 ราย) และการเกิดอันตรกิริยาต่อกันระหว่างยาที่เกิดจริงคิดเป็นร้อยละ 1.6 (5 ราย) ตามลำดับ จากการเก็บข้อมูลรายการยาในใบสั่งยาจำนวน 312 ใบ พบว่ายากันชักที่นิยมสั่งจ่ายมากที่สุดคือ phenobarbital (ร้อยละ 65.06), phenytoin (ร้อยละ 62.82) และ carbamazepine (ร้อยละ 41.67) ตามลำดับ ส่วนยาที่มักพบสั่งใช้ร่วมกับยากันชักมากที่สุดคือ folic acid (ร้อยละ 63.78), benzodiazepines (ร้อยละ 14.73) และ vitamin & mineral (ร้อยละ 12.18) ตามลำดับ การศึกษานี้ไม่พบว่ามีการเกิดอันตรกิริยาต่อกันระหว่างยากันชักที่มีความสำคัญทางคลินิกคือระหว่าง valprolic acid และ lamotrigine พบคู่ยาที่เกิดอันตรกิริยาต่อกันระหว่างยาที่อาจเป็นไปได้ด้วยกระบวนการทางเภสัชจลนศาสตร์จำนวน 32 คู่ยา โดยเกิดในขั้นตอนเมตาบอลิซึม ร้อยละ 90.63 ความรุนแรงอยู่ในระดับกลางร้อยละ 58.42 ความรุนแรงระดับเล็กน้อยร้อยละ 42.57 และไม่พบความรุนแรงในระดับสูง พบคู่ยาที่เกิดอันตรกิริยาต่อกันระหว่างยาที่อาจเป็นไปได้ด้วยกระบวนการทางเภสัชพลศาสตร์จำนวน 58 คู่ยา ส่วนใหญ่ร้อยละ 51.72 เป็นการเกิดอันตรกิริยาแบบเสริมกันและเพิ่มความเป็นพิษจากการใช้ยาโดยทั้งหมดมีความรุนแรงระดับเล็กน้อย ยาที่เกิดอันตรกิริยาต่อกันระหว่างยาแบบเกิดจริงกับยากันชัก คือ estrogens และ warfarin

ผู้ป่วยจำนวน 138 คนจากจำนวน 312 คน คิดเป็นร้อยละ 44.23 ได้รับการประเมินคุณภาพชีวิต โดยคุณภาพชีวิตในแง่ผลข้างเคียงจากการใช้ยาและคุณภาพชีวิตโดยรวมพบว่า กลุ่มที่มีแนวโน้มจะเกิดอันตรกิริยาต่อกันระหว่างยามีผลข้างเคียงจากการใช้ยาลดลงและมีคุณภาพชีวิตโดยรวมดีขึ้นภายหลังการติดตามการใช้ยา ($p = 0.864$ และ 0.045) ขณะที่กลุ่มที่เกิดอันตรกิริยาต่อกันระหว่างยาแบบเกิดจริงพบว่าคุณภาพชีวิตโดยรวมของผู้ป่วยลดลงอย่างมีนัยสำคัญทางสถิติ ส่วนคุณภาพชีวิตในแง่จิตสังคมพบว่า ภายหลังการติดตามการใช้ยากลุ่มที่มีแนวโน้มที่จะเกิดอันตรกิริยาต่อกันระหว่างยาและกลุ่มที่เกิดอันตรกิริยาต่อกันระหว่างยาแบบเกิดจริงมีแนวโน้มของคุณภาพชีวิตในแง่จิตสังคมดีขึ้นจำนวน 13 มิติและ 12 มิติ ตามลำดับ

ภาควิชา……เภสัชกรรม…….ลายมือชื่อนิสิต…….

สาขาวิชา…….เภสัชกรรมคลินิก……ลายมือชื่ออาจารย์ที่ปรึกษา……

ปีการศึกษา..……2546…….……...ลายมือชื่ออาจารย์ที่ปรึกษาร่วม……

4476632733 : MAJOR CLINICAL PHARMACY
KEY WORD : ANTIEPILEPTIC DRUGS / DRUG INTERACTION MONITORING

SERMSOOK JANTAI : DRUG INTERACTION MONITORING IN EPILEPTIC CLINIC AT NEUROLOGICAL INSTITUTE
THESIS ADVISOR : PORNANONG ARAMWIT, Pharm D., Ph. D.
THESIS COADVISOR : CHUTAMANEE SUTHESISANG, Ph. D.

This study was a descriptive and prospective research in epileptic clinic at neurological institute, during ten – month period from 1st June 2002 – 31st March 2003. The objectives were to determine the prevalence of drug interactions (DIs) of antiepileptic drugs (AEDs) and AEDs – other drugs, and to compare the quality of life (QOL) before and after drug interaction monitorings (DIMs) by pharmacist. Monitoring was performed at least 1 time and more than 1 month apart but no longer than 3 months. There were 312 subjects enrolled in this study. Incidence of DIs was 27.88% (87 cases), which can be devided into 2 categories; 26.28% (82 cases) of possible DIs (PDIs) and 1.60% (5 cases) of actual DIs (ADIs). Three hundreds and twelve prescriptions from 312 cases were enrolled to identify drug groups which favorable prescribed, the most favorable AED was phenobarbital (203 cases, 65.06%), phenytoin (196 cases, 62.82%) and carbamazepine (130 cases, 41.67%), respectively. Drugs which favorable prescribed with AEDs were folic acid (199 cases, 63.78%), benzodiazepines, vitamin & minerals and tricyclic antidepressants, respectively. The clinical importance interaction between AEDs, VPA and LTG, was not found in this clinic. In cases presented with PDIs, classified into 32 DDIs of pharmacokinetics interactions, the mechanism was metabolic processes (90.63%). The severity of DIs of 58.42% was moderate and 42.57% was minor and no severe case. Pharmacodynamic PDIs were classified into 58 of DDIs, the most common mechanism was additive interaction and combined toxicity (51.72%). The severity of all PDIs were minor. This study found that ADIs occurred during metabolic stage, pharmacokinetic interactions. Medications prescribed in cases of ADIs were estrogens and warfarin.

Patients 138 from 312 cases (44.23%) were enrolled for QOL assessment. In aspect of adverse events of AEDs and general health, PDIs group showed an improvement of QOL's score after DIMs by pharmacist ($p = 0.864$ and 0.045). But in ADIs group found that general health was declined significantly. In aspect of psychosocial, improved scores in 13 domains were observed in PDIs groups and 12 domains in ADIs, respectively.

Department……Pharmacy……..…Student's signature…….

Field of study……Clinical Pharmacy…Advisor's signature…….…..…..

Academic year….2003……..Co – advisor's signature…….

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LIST OF ABBREVIATIONS

AEDs	=	antiepileptic drugs
AUC	=	area under the curve
BP	=	blood pressure
BZPs	=	benzodiazepines
CBZ	=	carbamazepine
CNS	=	central nervous system
CYP	=	cytochrome
CZP	=	clonazepam
DIs	=	drug interactions
D-DIs	=	drug ─ drug interactions
DZP	=	diazepam
FMB	=	felbamate
GBP	=	gabapentin
HMG co-A reductase inhibitors	=	hydroxymethylglutaryl coenzyme A reductase inhibitors
LEV	=	levetiracetam
LTG	=	lamotrigine
LZP	=	lorazepam
mg	=	milligram
ml	=	milliliter
min	=	minute
MDZ	=	midazolam
No.	=	number
OCs	=	oral contraceptives
OXC	=	oxcarbazepine
PB	=	phenobarbital

PHT	=	phenytoin
PPIs	=	proton pump inhibitiors
QOL	=	quality of life
$t_{1/2}$	=	elimination half life
TCAs	=	tricyclic antidepressants
TPM	=	topiramate
TGB	=	tiagabine
SSRIs	=	serotoin reuptake inhibitors
μg	=	microgram
UGT	=	uridine diphosphate glucuronosyltransferase
VPA	=	valproic acid
VGB	=	vigabatrin
ZNS	=	zonisamide

CHAPTER I

INTRODUCTION

Background and Rational

Problem of drug interactions has been recognized as long ago as 1895, when Oliver and Schaefer reported that an adrenal extract could cause arrhythmias in dog anaesthetized with chloroform. Today, with increasing complexity of therapeutic agents available and widespread polypharmacy, the potential of drug interactions is enormous. Although many thousands of reports on adverse drug interactions appeared in biomedical literatures, only a relatively small number are clinically significant. Thus, the importance of drug interactions to clinical pharmacist primarily involves monitoring or predicting drug interaction likely to have clinically significant consequences, and, if so, the steps taken to avoid them, or prefered alternative treatments. In order to predict the possible consequences of co − administration of two or more drugs, it is essential for pharmacist to have a practical knowledge of the pharmacological mechanisms involved in drug interactions, an awareness of those drugs which are associated with the greatest risk of interaction, and of the most vulnerable patient groups.[1]

It is difficult to provide an accurate estimation of the prevalence of drug interactions, mainly because various studies used different criteria for definition (particularly in distinguishing between clinically significant and non − significant interactions). This has lead to widely discordant figures; it is estimated that between six to thirty percent of all adverse drug reactions are due to drug interactions. For example, a study in Australia found that 4.4 % of all adverse drug reactions which resulted in hospital admission were due to interaction.[2] Likewise, a retrospective chart review of 437 ADRs occuring during an 11- month period was conducted at a university hospital,

158 ADRs were directly related to hospital admission. Characteristic associated with these ADRs included documentation of 25% of drug – drug interaction (DDI). [3] Moreover, prevalence of potential DIs was determined in inhabitant of the Country of Funen (n = 471,732), it was found that 15% of population were exposed to drugs carrying of harmful interaction.[4]

In Thailand, several studies were conducted to determine the incidence of potential adverse drug interaction in outpatients prescriptions, the evalution is normally based on drug interactions database from "Drug interaction Facts" textbook and several relevant articles. The incidence of potential drug interactions varied between 32 – 43%.[5-8] However, only the study by Suwimon[9] concerns of actual drug interactions, it was performed only to inpatient admitted at medical wards of Phramongkutklao hospital. From these previous works, it is obvious that we should determine the actual drug interactions and outcome from the monitoring of potential adverse drug interaction, one of pharmaceutical care activities which should be performed in order to provide effective and safe medication use process.

The roles of pharmacist are extended beyond monitoring the compliance to more active partnerships with physicians in the optimization of drug therapy for epilepsy. Pharmacists can monitor drug or non-drug components of care, maintain and review patient medication profiles, and also screen for drug – drug interactions associated with antiepileptic drugs. Besides, pharmacists can obtain monthly seizure frequency data and document regarding lifestyle factors that affect seizures or quality of life in patient with epilepsy.

Epilepsy is a chronic disease that may require antiepileptic drug (AED) therapy for a long period of time.[10] The efficacy of AED monotherapy is well established.[11]

Approximately 60 – 70% of newly diagnosed patients have their seizures controlled effectively by one AED, and switching to an alternative AED will offer effective seizure control in up to half of the remaining 30 – 40% of patients. AED polytherapy may be helpful for small population of patients who do not respond to monotherapy, but careful consideration should be given to the consequences of any drug interactions between the various AEDs that are coadministered. Indeed, it is estimated that 6% of patients experiencing AED intoxication due to the drug interaction.[11] All new AEDs are given as add – on therapy in patients with chronic refractory partial epilepsy[12], resulting in initiation of polytherapy is the only option for new AEDs. Even when using AED monotherapy, patients may not be free of the consequences of potential drug interactions, as in many patients, concomitant diseases or other debilitating conditions may develop requiring the coadministration of non – AED drugs. The widespread use of the oral contraceptive pill by young women with epilepsy may result in unwanted drug interaction if it is administered with AEDs. Furthermore, patients with epilepsy, like many people, may use non-prescribed medications either intermittently or even throughout their lives, which may be associated with drug interactions. The therapeutic relevance of drug interactions is important not only when additional drugs are coadministered, but also when one or more drugs are removed from a multiple drug regimen. Interaction processes go into reverse when drug interaction is discontinued from a patient's drug regimen. Therefore, physicians must be aware that drug discontinuation may have a serious impact on the efficacy or toxicity of the remaining drugs as well.

It is now widely acknowledged that people with epilepsy are as likely to be distressed by social and cultural problems from continuing seizure, and that epilepsy has profound physical, psychological, and social consequences.[13] Although current seizure frequency is one of the most important predictors showing the efficacy of

treatment, it is not the only measure, especially from patient's viewpoint.[14] The effect of any diseases is determined by several factors, such as underlying biology, host factors, available medical interventions, and also by the attitudes and reactions of the surrounding society.[15] Quality of life is difficult to define but might be considered to reflect functions in these three main areas: physical, social, and psychological.[16] Devinsky and Cramer stated that the essence of quality of life was the balance between patients' and desired status.[17] It also is defined by how well one is able to function and how one feels about his daily life[18] , on the assumption that aspects of functional health status have an impact on quality of life. Although no definitive consensus has been reached concerning the essential nature of quality of life, there are some agreements that general health status is one of its main components.[19]

Because of the emphasis on the phenomenologic experience of the individual, it is necessary that quality of life is determined from the patient's subjective viewpoint, the physician's viewpoint being deliberately excluded, as self-reports are the primary method of assessing.[20] This criteria is set due to the fact that the evaluations conduct by physicians tend to concentrate primarily on seizure management while leaving all else as secondary features.[21] It has become relatively common to have patients make a judgment about their own medical care.[22] Patients must have the courage to express their opinions and show their dissatisfactions. There is a growing awareness of the psychosocial implications of epilepsy. People with epilepsy face social disadvantages not shared by those with other chronic diseases. Psychiatry problems, particulary anxiety, depression, and loss of self-esteem are common among people with epilepsy.[23-29] Most patients feel that a prospective employer's knowledge of a diagnosis of epilepsy will make it more difficult for them to get job.[30] Information on these issues come mainly from developed countries.[31] Very few studies originate from developing countries[32-33], and there is clearly a lack of documented evidence regarding the impact

of epilepsy in Thailand. Furthermore, there is no study on the improvement of quality of life due to intervention in drug – drug interaction monitoring by pharmacists, although several studies have defined decreasing of drug related problems increase quality of life.

Objectives

1. To determine the prevalence of possible and actual drug interactions of AEDs and AED(s) – other prescribed drug(s) based on drug interactions database from "Drug interaction Facts" textbook and several relevant articles.
2. To differentiate the adverse events of AEDs and quality of life between before – after drug interactions monitoring by pharmacist.

Benefits

1. To increase the awareness of importance of drug interactions in clinical setting.
2. To demonstrate the role of clinical pharmacist in the health care team.
3. The incidence of actual drug interactions should be decreased after screening drug interactions by pharmacists. Besides, the intervention suggested by pharmacists should be accepted by physicians in order to improve patients' quality of life.

CHAPTER II

RELATED LITERATURE REVIEW

I. Review of studies on drug interactions (DIs)

A number of studies on drug interactions, with many important differen--ces in design and methodology, attempt to estimate the incidence of drug interactions. The estimations of drug-drug interactions (D-DIs) are about 2.2% to 30.0% in hospital inpatients, 9.2% to 70.3% in community patients, and 0.2% to 8.0% of hospital admissions caused by D-DIs.[34-42]

In Thailand, estimated potential of DIs range from 11.4% to 50.0% in studies carried out in hospital inpatients, and from 4.22% to 32.0% in outpatients prescriptions review.[5-8,43-44] Many investigators base their conclusions on potential drug interactions and fail to consider whether patients actually experienced symptoms that could be attributed to them. On the basis of data availability, it is not accurately possible to define the incidence of clinically significant drug interactions.

A small numbers of widely used drugs are implicated consistently in DIs which are cyclosporin, digoxin, lithium, monoamine oxidase inhibitors, oral contraceptives, phenytoin, theophylline, and warfarin. They are usually potent therapeutic agents with narrow therapeutic index, where a small increase in plasma concentration may produce toxicity, e.g. digoxin, lithium and theophylline, or drug with a small decrease in plasma concentration may result in loss of therapeutic effect, e.g. carbamazepine and cyclosporin.

DIs may occur whenever two or more drugs are administered simultaneously. The DIs occur when one drug modifies the activity of another, either enhancing or

reducing its pharmacologic effect. The outcome may be beneficial if the therapeutic potency of the drug enhanced, or harmful when the interaction causes an increasing in the adverse effects of the drug or when a reduction in efficacy occurs. There are three basic types of DIs[41] as shown in Table 2.1

Table 2.1 Mechanisms of drug interactions

Pharmaceutical interactions
Occurring outside the patient (e.g. in infusion bottle or syringe), intravenous formulations and physical or chemical interactions
Pharmacokinetic interactions
Normally refers to the interactions in which one drug interferes with the disposition of another, alter the concentration of the drug at the site of action. These interactions are associated with a change in plasma concentration of either the drug or its metabolite(s) or both.
Absorption ; during passage of drug from the gastrointestinal tract to the blood stream.
Distribution ; during the passage of drug to its site of action (e.g. protein-binding displacement).
Metabolism ; during the biotransformation of a drug (enzyme inhibition or induction).
Excretion ; during excretion from the body, primary via the kidneys.
Pharmacodynamic interactions
It refers to the interactions occur between drugs that have similar or opposing pharmacologic mechanisms of action. These interactions take place at the cellular level where the drugs act and are not associated with any change in the plasma concentration of either drug.
Synergistic ; two drugs prescribed together produce a greater effect than the sum of their individual effects.
Antagonistic ; one of two prescribed together significantly reduce the effect of the other.

Pharmacokinetic and pharmacodynamic interactions will be discussed in this review since antiepileptic drugs (AEDs) – drug(s) interactions involve these pathways.

II. Pharmacokinetics interactions of AEDs

Pharmacokinetics interactions can occur during any stage of drug disposition (i.e., during absorption, distribution, metabolism, or elimination), and they are associated with drug-concentration changes in the peripheral plasma compartment. They also may take place, in the case of centrally acting agents such as AEDs, in the central brain compartment (e.g., cerebrospinal fluid or the extracellular fluid site of drug action). Pharmacokinetics interactions taken place in the brain central compartment are currently very difficult to measure in human and may be confused with pharmacodynamic interactions.

Absorption. Absorption is the entry of drug molecules into the systemic circulation via the mucous membranes of the gut or lungs, via the skin, or from the site of an injection. DIs of AEDs are rare during absorption, although antacids have been shown to reduce the absorption of some AEDs (e.g.,phenytoin (PHT), phenobarbital (PB), carbamazepine (CPZ), gabapentin (GBP)) by decreasing the acidity of the stomach and also by formation of insoluble complex.

Distribution. Distribution is the movement of drug molecules between water, lipid, and protein compartments in the body, including the movement of drugs to their sites of action, metabolism, and elimination. Interactions involving the distribution of drugs are difficult to ascertain. After about 1 month of coadministration vigabatrin (VGB) with PHT, the plasma concentration of PHT decreased only 30%. To date, the mechanism of this interaction remains unknown, although it is thought to involve an effect on PHT distribution.[45]

As drugs enter in various portions to the systemic circulation, they can bind to plasma proteins, for example, PHT, diazepam (DZP), valproic acid (VPA), and tiagabine (TGB) are more than 90% protein bound. High protein binding drugs compete

for protein binding, resulting in a displacement of AEDs from their plasma protein-drug complex, and increasing in the free fraction (unbound concentration/total concentration) of the previously protein-bound AED. The unbound drug is available to interact not only with pharmacologic receptors but also with hepatic drug-metabolising enzymes. As the free fraction of the drug increases, the body has tendency to eliminate more drugs out of the system, leading to a decline in total drug concentration. Unbound (pharmacologically active) drug concentrations are dependent on drug dose and hepatic intrinsic clearance. Therefore, at steady state, a displacement interaction may transiently increase the unbound drug concentration, the concentration should return to its preinteraction value, assuming there has not been any alteration in hepatic intrinsic clearance. In practice, these interactions are potential clinical significance in that they confound therapeutic drug monitoring. It is important to guide dosing strategies by monitoring free drug concentrations. When PHT and VPA are coadministered, a complex interaction can occur including both a displacement of PHT from its plasma protein-binding sites and inhibition of PHT metabolism. The increasing in plasma PHT concentration can lead to toxicity in some patients. Felbamate (FBM), GBP, lamotrigine (LTG), levetiracetam (LEV), topiramate (TPM), and VGB are not significantly bound to plasma proteins and are not subject to this type of drug interaction.

Elimination. Elimination is the removal of drug molecules from the body by excretion, usually by the kidneys, or by biotransformation/metabolism (primarily by the cytochrome (CYP) P450 system), mainly in the liver. Excretion is important for water-soluble drugs and the water-soluble metabolites of lipid-soluble drugs. Conjugation, another metabolic process involving hepatic uridine diphosphate glucuronosyltransferase (UGT) enzymes, usually result in the production of pharmacologically inactive and less lipid-soluble metabolites, which are often excreted

in the urine or in the bile. Although DIs affecting renal excretion are rare with AEDs, other drugs are reported to interact at this site.

Metabolism. Metabolism is the most important mechanism of elimination and accounts for the majority of clinically relevant drug interaction with AEDs. Metabolic pathway such as conjugation involving UGTs (for example, LTG and VPA) and β-oxidation (for example, VPA) are relevant, but the CYP P450 system is by far the most important system for AED metabolism (for example, PHT, PB, CBZ, TPM, TGB, zonisamide (ZNS), and felbamate (FBM)).

III. CYP P450 enzymes and AED interactions

CYP P450 enzymes are major component of the mixed-function oxidase system that is located in the smooth endoplasmic reticulum of the cells almost in all tissues. The highest concentrations of CYP enzymes are found in the liver, and these enzymes are responsible for the metabolism of not only exogenous chemicals (xenobiotics), but also endogenous substances (e.g. corticosteroids). PB, PRM, and CBZ are inducers of CYP isoenzymes, whereas VPA is an inhibitor. Although *in vitro* screening allows prediction to be made about potential drug interactions, it is not possible to anticipate the exact magnitude of a particular interaction, and this still has to be determined by clinical investigation.

A number of problems experienced with AEDs are due to DIs with PHT. PHT is associated with more DIs than any other AEDs. PHT binds loosely to CYP isoenzymes and is easily displaced by other drugs, therefore its metabolism is inhibited. Furthermore, the fact that the metabolism of PHT is saturable makes PHT susceptible to problematic interactions. The isoenzyme CYP2C9 is responsible for 80% of the metabolism of PHT, the remaining 20% being metabolised by CYP2C19. If a

concomitantly administered drug interacts with CYP2C9, such as amiodarone, it will have a greater effect on the plasma concentration of PHT compared with a drug that interacts with CYP2C19 such as cimetidine.

Interaction involving the induction of CYP isoenzymes becomes apparent more slowly than those resulting from inhibition. Induction requires the synthesis of new protein, and it may take several days or weeks before clinical effects will be observed. When enzyme inhibition is involved, the time of the interaction depends on the elimination half-life of the affected drug, with potentiation of drug activity occurring more quickly if the drug has a short-life. For example, LTG and PB have half-life values of 1.5 and 4 days, respectively, and therefore their maximal potentiations occur 7.5 and 20 days later, respectively. If DIs result in an increase plasma concentration of a drug or its active metabolites, then patients may experience toxicity and side effects, in which case, it may be necessary to reduce the dose of the affected drug. However, in some patients, an increase in plasma drug concentration may actually enhance the therapeutic response, particularly if the concentration is previously subtherapeutic. An extended half-life may also mean that the frequency of dosing can be reduced, which may help to improve the compliance. In contrast, if DIs involving the metabolism to coadministered drugs result in a reduction in the plasma concentration of the affected drug or its active metabolite, there may be a reduction in efficacy and a dosage increase may be required.

Because most clinically important interactions involving AEDs are the consequence of alterations in drug metabolism, an AED that does not undergo metabolism or alter the activity of hepatic enzymes is less likely to be involved in metabolic interactions. AEDs that are not metabolised or undergo minimal metabolism include GBP, LEV, and VGB.

IV. Pharmacokinetic profiles of new AEDs versus established AEDs

The ideal pharmacokinetics for an AED are good oral bioavailability, a half-life of 12-24 hour that allows once-daily or twice-daily dosing, linear kinetics so as to minimize inter-and intrapatient, minimal plasma protein binding so as to minimize the potential for plasma protein-displacement interactions and to make the interpretation of plasma-concentration monitoring less complicated, no metabolism so as to minimize the potential for DIs and the production of pharmacologically active metabolites, and no drug interaction.[46] The appreciation of these pharmacokinetic goals result in more rational drug design. AEDs with simple pharmacokinetic characteristics allow more rational prescribing of multiple drug therapy, which should result in an increase efficacy and reduce toxicity. The pharmacokinetic profiles of the currently available AED and AEDs drug interactions involving CYP P450 are shown in Table 2.2 and Table 2.3, respectively.

Table 2.2 Pharmacokinetic profiles of AEDs [47]

AEDs	Linear Kinetics	Nonlinear Kinetics	Plasma protein binding(%)	Elimination half-life(h) coadministered with a non-interacting drug	Elimination half-life(h) coadministered with an AED cytochrome P450 inducer	Elimination half-life(h) coadministered with an AED cytochrome P450 inhibitor
First-generation AEDs						
Carbamazepine		yes[a]	75	16-24	9-10	A
Clobazam	yes		85	10-58	<10-58	A
Clonazepam	yes		85	19-40	<19-40	A
Diazepam	yes		98	24-48	16-32	A
Ethosuximide	yes		0	40-60	34-56	A
Phenobarbital	yes		50	80-100	80-100	>80-100
Phenytoin		yes[b]	90	7-42[f]	<7-42	>7-42
Primidone	yes		25	8-12	3-11	A
Valproate		yes[C]	90	8-18	2-12	A
Second-generation AEDs						
Felbamate	yes		25	13-23	14	A
Gabapentin		yes[d]	0	5-9	-	-
Lamotrigine	yes		56	22-38	14-15[g]	70[h]
Levetiracetam	yes		0	6-8	-	-
Oxcarbazepine	yes		40	5-30	6-19	5-28
Tiagabine	yes		98	5-8	2-5	A
Topiramate	yes		15	19-25	9-12	A
Vigabatrin	yes		0	5-7	4-6	A
Zonisamide		yes[e]	60	57-68	27-37	-

A.half-life values have not been formally investigated, but plasma levels would be expected to be increased during combination therapy; - , no data available, but an effect is not expected; AED, antileptic drug.

[a] Due to autoinduction.

[b] Due to saturation of metabolism.

[c] Due to saturation of plasma protein binding.

[d] Due to saturation of gastrointestinal absorption.

[e] Refer to MHD metabolite(see table 1)

[f] Dose or plasma concentration dependent

[g] Glucuronidation induced

[h] Glucuronidation inhibited

Table 2.2 was modified from Patsalos PN. Fröscher W, Pisani F, van Rijn CM. The importance of drug interactions in epilepsy therapy. Epilepsia 2003; 43(4): 365 – 385.

Table 2.3 AED drug interactions involving the cytochrome P450 system [47]

		Cytochrome P450 isoenzyme associated with AED metabolism							
			CYP families						
		CYP 1	CYP 2						CYP 3
AED	Metabolism	CYP1A2	CYP2A6	CYP2B	CYP2C8	CYP2C9	CYP2C19	CYP2E1	CYP3A4
First-generationAEDs									
Carbamazepine	Cytochrome P450	Substrate	NA	NA	Substrate	Inducer	Inducer? Inhibitor?	NA	Substrate Inducer
Clobazam	Cytochrome P450	-	-	-	-	-	-	-	-
Clonazepam	Cytochrome P450	-	-	-	-	-	-	-	Substrate
Diazepam	Cytochrome P450	-	-	Substrate?	-	-	Substrate	-	Substrate
Ethosuximide	Cytochrome P450	-	-	Substrate	-	Substrate?	-	Substrate	Substrate
Phenobarbital	Cytochrome P450	Inducer	-	Inducer	Inducer	Substrate? Inducer	Substrate? Inducer	Substrate	Inducer
Phenytoin	Cytochrome P450	Inducer	NA	Inducer	Substrate	Substrate? Inducer	Substrate? Inducer	NA	Inducer
Primodone	Cytochrome P450	Inducer	-	Inducer	Inducer	Substrate? Inducer	Substrate? Inducer	Substrate	Inducer
Valproate	Cytochrome P450 glucuronidation (UGT),B-oxidation	NA	Substrate	-	-	Substrate Inhibitor	Substrate	NA	Substrate? Inhibitor?
Second-generationAEDs									
Felbamate	CytochromeP450	-	NA	-	-	-	Inhibitor	Substrate	Substrate Inducer
Gabapentin	Not metabolised	-	-	-	-	-	-	-	-
Lamotrigine	Glucuronidation (UGT)	-	-	-	-	-	-	-	-
Levetiracetam	Nonhepatic Hydrolysis	NA	NA	-	-	NA	NA	NA	NA
Oxcarbazepine	Glucuronidation MHD(UGT) And limited CytochromeP450 Metabolism of MHD	-	-	-	-	-	Inhibitor	-	Inducer
Tiagabine	CytochromeP450	-	-	-	-	-	-	-	Substrate
Topiramate	CytochromeP450 Glucuronidation(UGT)	NA	NA	NA	NA	NA	Inhibitor	NA	NA
Vigabatrin	Not metabolised	NA	NA	NA	NA	NA	NA	NA	NA
Zonisamide	Primarily CytochromeP450	NA	NA	-	-	NA	NA	NA	Substrate

NA,not attected; - ,no data available ;MHD,10,11-dihydro-10-hydro-5H-dinenzoazepine-5-carboxamide(the primary pharmacologically active metabolite of oxcarbamazepine);AED,antiepileptic drug;UGD,uridine diphosphate glucuronosyl tramsferase.

Table 2.3 was modified from Patsalos PN. Fröscher W, Pisani F, van Rijn CM. The importance of drug interactions in epilepsy therapy. Epilepsia 2003; 43(4): 365 – 385.

Of the nine established AEDs, CBZ, VPA, and PHT are associated with nonlinear pharmacokinetics. In contrast, most of the new AEDs such as LTG, LEV, oxcarbamazepine (OXC), TGB, and TPM exhibit linear pharmacokinetics (Table 2.2). Some of the second-generation AEDs are not metabolised and undergo renal elimination, which results in less pharmacokinetic variability and a lower potential for DIs (for example, VGB, LEV, and GBP). Furthermore, many of the second-generation AEDs (for example, LTG, LEV, GBP, and VGB) do not induce or inhibit enzymes involved in drug metabolism.[48]

V. Pharmacodynamic interactions

Pharmacodynamic interactions result in a modification of the pharmacological action of a drug without an alteration in its plasma or central nervous system (CNS) concentration. Pharmacodynamic interactions can take place directly at the site of action of the drug (e.g. synergistic or antagonistic effects at the target receptor) or indirectly by interfering with other physiologic mechanisms. A pharmacodynamic interaction can be useful when efficacy is additive and toxicity is infraadditive. However, pharmacodynamic interactions are more difficult to identify and measure than pharmacokinetic interactions and are often only concluded by default when a pharmacokinetic interaction has been ruled out. Animal studies provide useful evidence of pharmacodynamic interaction involving AEDs, and results from *in vitro* studies are promising, although there is still little evidence of the applicability of such interactions in human.[49] However, clinical experiences show that some combinations of AEDs are more effective in controlling seizures than either drug used alone, and such combinations will be used despite a lack of scientific evidence to explain the favorable drug interaction.[50] Examples of these AED combinations include clonazepam (CZP) plus VPA[50], and CBZ plus VPA.[50] Similar enhancement in clinical efficacy is also reported for combinations of newer AEDs such as TGB and VGB[51], VGB and LTG[52],

LTG and TPM[53], or VPA and LTG.[54] Low dose of LTG coadministered with VPA appears to produce a therapeutically desirable pharmacodynamic interaction inpatients with typical absence seizures.[54] However, the possibility that some of these therapeutic enhancements result from pharmacokinetic interactions taking place in the central brain compartment, rather than as a result of pharmacodynamic interactions, cannot be ruled out at this time.

VI. Clinically relevant drug interactions

A number of factors must be considered when patients are administered multiple AEDs (Figure 2.1). The most clinically important AED-AED interactions that may affect the clinical management of patients with epilepsy are shown in Table 2.4.
It is acknowledged that many other drug interactions occur in selected patients under certain circumstances or are observed infrequently, but are nevertheless important to individual patients. Plasma drug concentration determinations should be undertaken at the time of the clinical event (e.g., patient complaining of side effects) and the drug dosage adjusted accordingly. In the situation in which the clinical status of the patient is unaffected, plasma drug concentration levels should be determined under steady-state conditions, ideally just before the next dose ingestion (trough). Clinical guidance on how to manage the use of multiple AEDs in patients with epilepsy is provided in Figure 2.2.

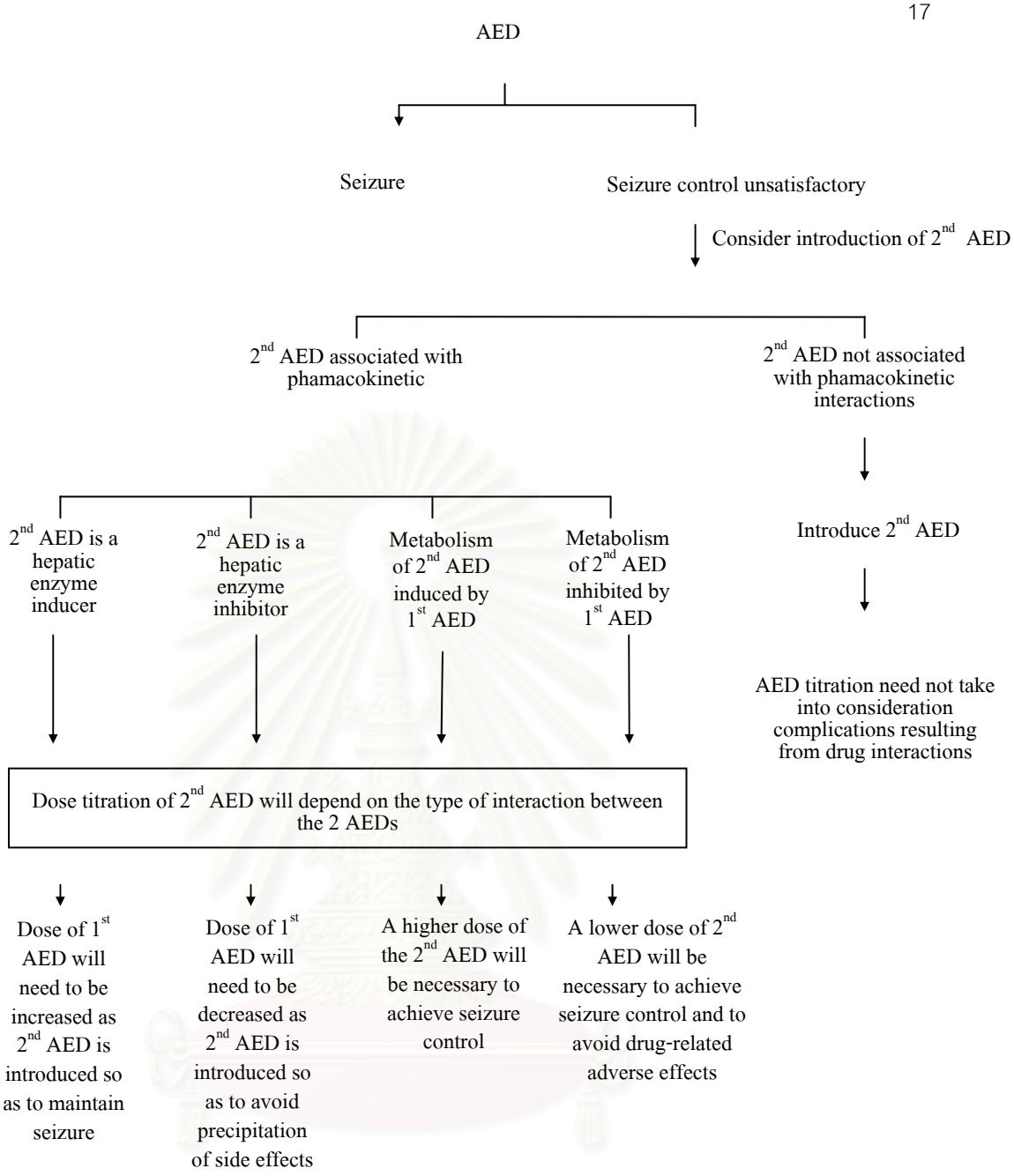


FIGURE 2.1 Drug-interaction considerations in antiepileptic drug (AED) polytherapy[47,49]

TABLE 2.4 Clinical outcome of AED and non-AED interactions[42,47,66]

Non-AED	AED	Pharmacologic Outcome of drug interaction	Potentially clinically relevant outcome of the drug interaction
Oral contraceptive pill	Enzyme-inducing AEDs (CBZ,PHT,PB,FBM, TPM)	Increased metabolism of the contraceptive pill and reduced hormone levels	Pregnancy
Theophylline	Enzyme-inducing AEDs	Increased metabolism of theophylline	Reduced efficacy against asthma and chronic bronchitis
Dicoumarol/warfarin	Enzyme-inducing AEDs	Increased metabolism of dicoumarol/warfarin and reduced anticoagulant activity	Decreased anticoagulant activity could be life threatening. If the AED is subsequently removed, there is the risk of dicoumarol /warfarin toxicity (e.g., haemorrhage)
Digoxin	PHT,TPM	Decreased plasma concentration of digoxin	Reduced efficacy in cardiac failure
Corticosteroids	Enzyme-inducing AEDs	Increased metabolism of the corticosteroid	Reduced therapeutic effects. May need to increase the dose of the corticosteroid
Antacids	PB,PHT,CBZ,GBP	Reduced gut absorption of AEDs	Reduced efficacy of the AEDs and seizure exacerbation
Omeprazole	PHT	Inhibition of PHT metabolism	If experiences PHT toxicity, PHTdose reduction will be necessary
Cimetidine	PHT	Inhibition of PHT metabolism	If experiences PHT toxicity, PHT dose reduction will be necessary
Tricyclic antidepressant (TCAs)	Enzyme-inducing AEDs	Bidirectional interaction with TCA concentrations reducing and AED concentrations increasing	Reduced efficacy of the TCAs and possible toxicity of the AEDs
Benzodiazepines	CBZ,PHT,PB	Increases metabolism and decreased plasma concentrations of benzodiazepines	Adjust doses if necessary

Table 2.4 (continued) Clinical outcome of AED and non-AED interactions[42,47,66]

Non-AED	AED	Pharmacologic Outcome of drug interaction	Potentially clinically relevant outcome of the drug interaction
Fluoxetine	CBZ,PHT	Inhibition of AED metabolism and increased plasma concentrations of CBZ and PHT	Initiate at or lower the dose of CBZ/PHT to the lower end of the therapeutic dose range. Look for signs of CBZ/PHT toxicity (e.g., dizziness)
Sertraline	LTG	Inhibition of AED metabolism and increased plasma concentrations of LMG	Look for the signs of LTG toxicity, and reduce the dose of LTG if necessary
Haloperidol	Enzyme-inducing AEDs	Increases metabolism of haloperidol with a subsequent decrease in plasma concentration	Should monitor the plasma concentrations of haloperidol and adjust the dose if necessary
Fluconazole	PHT	Inhibition of PHT metabolism with a possible increase in PHT plasma concentrations	If experiences PHT toxicity, PHT dose reduction may be necessary
Griseofulvin	Enzyme-inducing AEDs	Increases metabolism of griseofulvin and reduced plasma concentrations	Reduced antifungal activity
Erythromycin	CBZ	Inhibition of the metabolism of the AEDs and increased plasma concentrations	Observe for signs of AED toxicity and, if necessary, reduce the dose
Clarithromycin	CBZ	Inhibition of AED metabolism and increased plasma concentrations of CBZ	If coadministered, monitor for signs of CBZ toxicity. Reduce the dose if necessary

Table 2.4 (continued) Clinical outcome of AED and non-AED interactions[42,47,66]

Non-AED	AED	Pharmacologic Outcome of drug interaction	Potentially clinically relevant outcome of the drug interaction
Antiviral agents that are metabolized by CYP3A4	Enzyme-inducing AEDs	AEDs can increase the metabolism and reduce the plasma concentrations of antiviral agents	Reduced efficacy, increased viral replication, and the development of resistance
Cyclosporine	Enzyme-inducing AEDs	AEDs can increase the metabolism and reduce the plasma concentrations of cyclosporine	Reduced immunosuppressant activity. Increase the dose of cyclosporine is necessary.
Anticancer agents	Enzyme-inducing AEDs	AEDs can increase the metabolism of anticancer agents and reduce therapeutic efficacy	Reduced efficacy of the anticancer agent and the potential for a poorer outcome for the patient

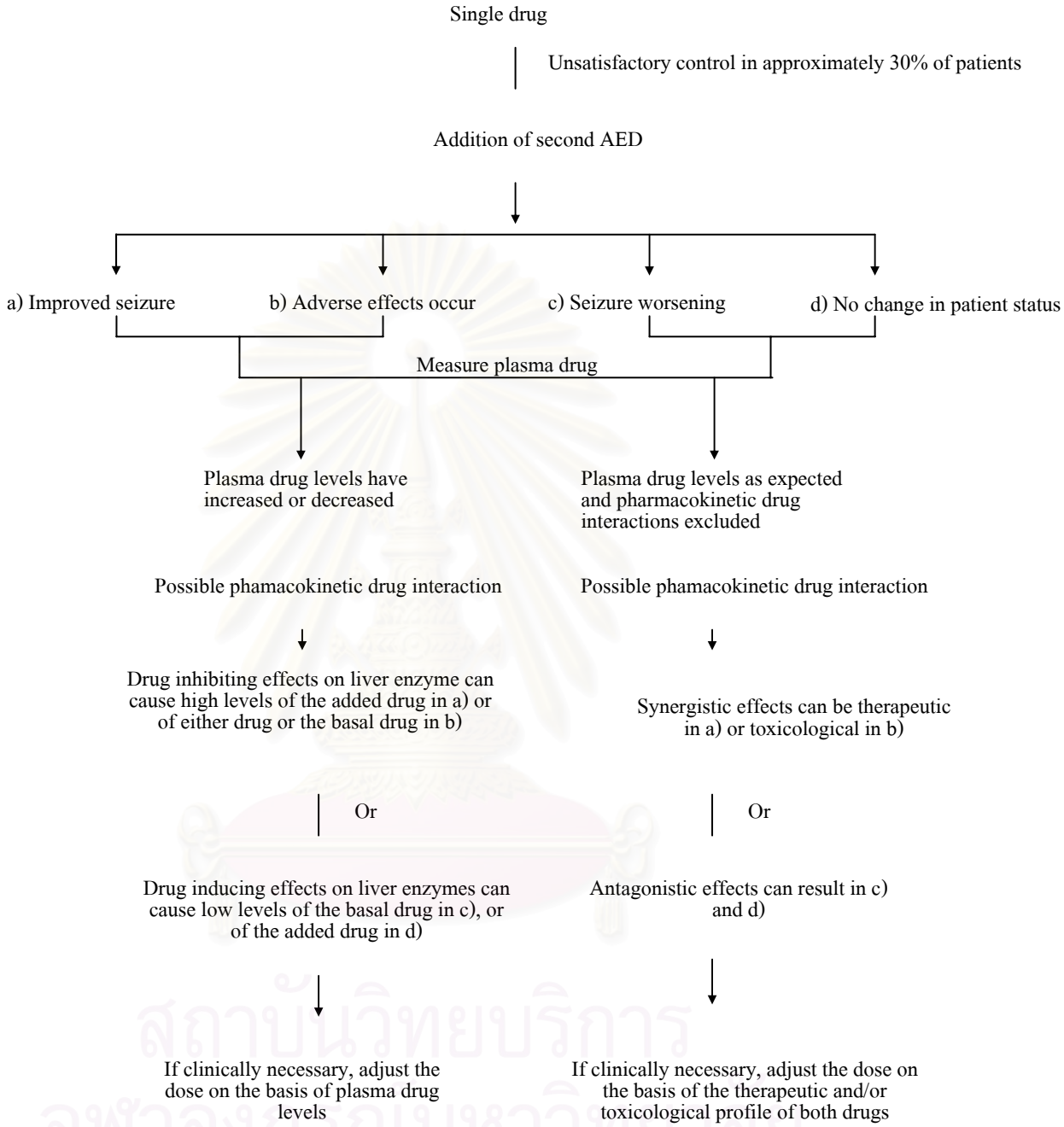


FIGURE 2.2 Impact of antiepileptic drug (AED) interactions on therapeutic outcome[47,49]

VII. AED-AED interactions

VPA, LTG, TPM, TGB and OXC coadministered with enzyme inducing AEDs

PB, PHT, and CBZ are potent enzyme inducers, capable of increasing the level of activity of various cytochrome P450 and UGT isoenzymes[55] (Table 2.2). This usually results in an increase in the rate of metabolism of the affected coadministered drug, followed by a decrease in the plasma concentration of the coadministered drug, and possibly a loss of clinical efficacy. The amount of enzyme induction is dependent on the dose of the inducing drug, and consequently the coadministration of multiple enzyme inducers can have a significant effect, particularly if they induce common P450 isoenzymes.

When PB, PHT, or CBZ are coadministered with either VPA, LTG, TPM, or TGB, they induce an increase in the metabolism of these drugs and a subsequent reduction in their half-lives. It may be necessary to increase the dose of the affected AED to maintain clinical efficacy with the combination therapy. Generally the discontinuation of enzyme-inducing AEDs also should be considered when treating patients with epilepsy. For example, in the case of TPM, the discontinuation of CBZ or PHT from a regimen leads to an increase in the plasma concentration of TPM.[56]

LTG coadministered with VPA

VPA is an enzyme inhibitor, capable of reducing the rate of metabolism of the coadministered drug. Coadministration of VPA and LTG, VPA competes with LTG for glucuronidation (a conjugation reaction).[57] The inhibition of LTG metabolism, increases the half-life of LTG from 30 to 59 hour, and increases the plasma concentration of LTG. The reduction of LTG dosage may avoid the problems with

toxicity, particularly cutaneous skin rash. In clinical practice, the introduction of LTG to a patient already taking VPA should be undertaken with caution, a lower LTG dose and slower dose titration is undertaken compared with those in patients coprescribed enzyme-inducing AEDs (e.g. PHT, PB, and CBZ). However, there is no risk of rash if VPA is introduced to patient already stabilised with LTG.

PB coadministered with VPA[47]

The metabolism of PB is reduced (by inhibiting CYP2C9) when VPA is coadministered with PB, resulting in an increase in plasma PB concentration. This pharmacokinetic interaction is clinically important since it occurs in most patients receiving the combination therapy and may lead to sedation and drowsiness. In order to decrease the toxicity, the dose of PB may need to be reduced in 80% of patients when it is coadministered. It should be noted that this interaction has highly variable outcomes in different patients, and this is dependent on the concentration of PB. Besides, in some patients, stupor or coma (VPA-induced encephalopathy) may occur in patients using this combination and can occur without a significant elevation of the plasma concentrations of PB, the mechanism of this interaction is currently unclear.

PHT coadministered with VPA[47]

Because unique characteristics, DIs with PHT are frequently observed. PHT is substantially, but loosely, bound to plasma proteins. It is also extensively metabolised by, but loosely bound to, cytochrome P450 enzymes. These characteristics make it prone to competitive displacement and inhibitory metabolic processes. In addition, the metabolism of PHT is saturable at plasma concentrations associated with seizure control. Therefore a slight inhibition of metabolism can lead to disproportionate increase in drug concentration and a risk of toxicity. VPA can both displace PHT from its plasma protein-binding sites (albumin) and weakly inhibit PHT metabolism. Commonly, this complex interaction, which results in a reduction in total plasma PHT

concentration, does not adjust any PHT dose because the unbound (pharmacologically active) concentration is unaffected. In the case of a need to adjust the dose of PHT, adjustment should be guided by measurement of free PHT concentrations in plasma. However, adding VPA to a PHT regimen may lead to elevation of both total and free PHT concentrations and cause intoxication in some patients. If the patient experiences toxicity, the dosage of PHT should be reduced. Other drugs that interact with PHT in the same manner of VPA include phenylbutazone, tolbutamide, and amiodarone.

CBZ coadministered with VPA

CBZ is completely metabolised to CBZ-10,11-epoxide and then to CBZ-10-11-diol by cytochrome P450 enzymes. CBZ is an enzyme inducer, and its own metabolism is susceptible to autoinduction after repeated administration. VPA increases the plasma concentration of the epoxide metabolite by inhibiting epoxide hydrolase, without any marked changes in the concentration of CBZ.[58] The clinical significance of this interaction is important in children, in whom concentrations of epoxide less than 13 μg/ml have been observed, along with severe side effects such as vomitting and tiredness. Some clinical evidences show regarding the synergistic pharmacodynamic interaction between CBZ and VPA in complex partial seizure.[59]

CBZ coadministered with PB

Concomitant administration of the enzyme-inducing AED, PB increases the metabolism of CBZ and reduces CBZ plasma concentrations. The consequence of this interaction reduces CBZ efficacy. Interestingly, when PRM (which is metabolished to PB) is coadministered with CBZ, there is a concurrent decrease in CBZ and increase in CBZ-epoxide (the pharmacologically active metabolite of CBZ) plasma concentrations. This may result in both reduced efficacy and toxicity, and CBZ dose adjustment guided by the monitoring of plasma epoxide concentrations may be useful if toxicity occurs.

CBZ coadministered with LTG [47]

The combination therapy with CBZ and LTG can result in pharmacodynamic interaction causing neurotoxic symptoms such as headache, nausea, dizziness, and ataxia. It may be necessary to reduce the dose of CBZ if toxicity occurs.

PHT coadministered with TPM

TPM reduces the clearance of PHT in some patients and lead to increasing in plasma concentration and elevation of PHT induced toxicity. The reduction in the dose of PHT should be considered if patients experience toxicity.

PHT coadministered with OXC

OXC inhibits the isoenzyme CYP2C19. Consequently, during comedication with PHT, PHT plasma concentrations can increase up to 40%, leading to toxicity, particularly in patients using high dose of OXC. PHT dosage should be adjusted in these patients.

PB coadministered with PHT

PB and PHT are metabolised by the same phenylhydroxylating system, therefore they may inhibit each other's metabolism. This bidirectional drug interaction is complex and can lead to unpredictable changes in drug concentration. Low doses of PB induce the metabolism of PHT, thus reducing its concentration. However, higher doses of PB competitively inhibit PHT metabolism and increase PHT concentrations.

VIII. AED and non-AED interactions

The most clinically important AED and non-AED drug interactions that may affect the clinical management of patients with epilepsy have been discussed earlier in Table 2.4.

Oral contraceptives

The enzyme-inducing AEDs, PB, PHT, CBZ, and PRM, are capable of increasing level of activity of various cytochrome P450 isoenzymes (Table 2.2), which may accelerate the hepatic metabolism of oral contraceptives. The consequence of the drug interaction is a potential reduction in contraceptive efficacy, particularly with low-dose estrogen oral contraceptives, and increased risk of unwanted pregnancy. It may be necessary to increase the dose of estrogen to more than 50 μg when oral contraceptives are used concomitant with enzyme-inducing AEDs.[60] Women with epilepsy who choose to use oral contraceptives should be advised also to use the second method of contraception such as a cap, condom, or diaphragm.

Available data suggests that the second-generation AEDs are less likely to have unfavourable DIs with oral contraceptive agents.[61] It is reported that GBP, LTG, LEV, TGB, and VGB can be administered with oral contraceptives without the risk of contraceptive failure.[61] Women receiving FBM, OXC, and TPM should be advised to use additional barrier methods of contraception and may benefit from higher dose of estrogen, as these AEDs are shown to have some enzyme-inducing activity. For TPM, although the mechanism of the effect on ethinyl estradiol is not known, induction of CYP3A4 does not appear to be involved.[62] There is insufficient evidence regarding the interaction between ZNS and oral contraceptives, care should be taken to prevent unwanted pregnancy when using combination.

Theophylline

Theophylline is indicated for the management of bronchospasms in reversible airway obstruction associated with stable asthma and chronic bronchitis. Theophylline is metabolised by hapatic enzymes (primarily CYP1A2, but CYP2E1 also is involved) and the enzyme-inducing AEDs, PB, PHT, CBZ, and PRM are capable of increasing the metabolism of this drug, in which case, an increase in the dose of

theophylline may be necessary.[63] The second-generation AEDs, such as VGB, LTG, TGB, LEV and GBP, which do not induce CYP isoenzymes, are unlikely to interact with theophylline.

Dicoumarol and Warfarin

Dicoumarol is an anticoagulant indicated for the prevention of thrombosis associated with cardiovascular diseases and surgical procedures for vascular disease. Dicoumarol interferes with coagulation by competitively binding to vitamin K, which is essential for the formation of several coagulation factors. Warfarin is an anticoagulant that is therapeutically similar to dicoumarol. Enzyme-inducing AEDs such as PB, PHT, and CBZ can reduce the anticoagulant effects of both drugs by increasing their metabolism possibly via an induction of CYP2C9. It must be taken to maintain appropriate plasma concentrations of dicoumarol/warfarin during polytherapy, as significant changes in plasma concentration could be life-threatening. This can be achieved by checking patient's coagulation function. The effects of discontinuing a concomitantly administered AED also should be considered. This is particularly important if the AED is removed or replaced by one that does not induce hepatic enzymes, because the loss of enzyme induction may lead to haemorrhage due to elevated dicoumarol/warfarin plasma concentration. As drug interactions with dicoumarol/warfarin are dependent on the CYP system, the second-generation AEDs that do not induce CYP isoenzymes (e.g. VGB, LTG, TGB, LEV, and GBP) are unlikely to interact with dicoumarol/warfarin. In addition, OXC does not appear to interact with warfarin to any clinically relevant extent.[64]

Digoxin

Digoxin, the most frequently prescribed cardiac glycoside, is indicated for the management of chronic cardiac failure. Digoxin is excreted mainly by filtration in the kidneys without being metabolised. Consequently, interactions with digoxin

relate mainly to effect on renal excretion, tissue and plasma protein binding, distribution within the body, alterations in gut absorption, and pharmacodynamic sensitivity to digoxin and other digitalis glycosides. Concomitant administration of digoxin with PHT may result in reduced plasma concentrations of digoxin and unfavorable effect on the management of cardiac failure. Physicians are advised to check the plasma digoxin concentration and to adjust drug doses accordingly as a result of the narrow therapeutic index of digoxin. TGB, the most protein bound of the second-generation AEDs, does not have any clinically significant effect on the plasma concentration of digoxin. Coadministration of TPM and digoxin may result in a small reduction in the plasma concentrations of digoxin, although the mechanism of the interaction is uncleared.[65] The study of pharmacokinetic interactions in healthy adults showed no pharmacokinetic interaction between LEV and digoxin.[65]

Corticosteroids

Corticosteroids are indicated for hormone replacement and in the management of inflammatory disorders such as rheumatoid arthritis, fever, ulcerative colitis, Crohn's disease, and chronic active hepatitis. The enzyme-inducing AEDs (PB, PHT, and CBZ) may increase the metabolism of corticosteroids and reduce their therapeutic efficacy. If the physician observes a lack of therapeutic response in a patient receiving polytherapy then the dosage of corticosteroid may need to be increased.[66] AEDs that do not induce hepatic CYP isoenzymes such as VGB, LTG, TGB, LEV, ZNS, and GBP are unlikely to interact with corticosteroids.

Antiulcer drugs

If the dissolution process of an orally administered drug is dependent on the acidity of the gut, the absorption may be altered considerably by the coadministration of drugs that modify the pH of the stomach. Antacids (e.g. aluminium hydroxide and calcium carbonate) rapidly raise gastric pH. In general, the alteration in

gastric pH does not result in clinically important drug interactions, as the absorption of most drugs is not affected by a less acidic pH in the gut.[66] Antacids show to reduce the plasma concentrations of PB, PHT, CBZ, and GBP.[66]

Omeprazole is a proton-pump inhibitor whose action blocks the release of gastric parietal cells. It provides effective treatment of gastric and duodenal ulcers and is the drug of choice for the treatment of oesophageal reflux disease. Omeprazole can increase PHT plasma concentrations by inhibiting CYP2C19, resulting in toxicity. If omeprazole is subsequently removed from a PHT-based regimen without an approximately PHT dose adjustment, seizure may recur because of the reduction in plasma concentration of PHT. [66]

Cimetidine, a histamine H_2-receptor antagonist that rapidly reduce the basal and stimulate secretion of gastric acid and pepsin, is indicated for the treatment of duodenal and gastric ulceration and other conditions in which the reduction of gastric acid production is beneficial. It is also an inhibitor of cytochrome P450 isoenzymes CYP2C9, CYP2D6 and CYP3A4, and is capable of prolonging the half-lives of those AEDs that would normally be metabolised by these isoenzymes (e.g. PHT and CBZ). The inhibitory effect of cimetidine on CYP3A4 is not substantial, and the interaction with CBZ is of modest clinical significance.[66] PB and PRM also are metabolised by CYP2C19 and may be affected by coadministration with cimetidine. The interaction of cimetidine and PHT is of clinical significance, monitoring of patients prescribed both agents is recommended, with the dose of PHT being reduced if necessary. None of the second-generation AEDs is a substrate for either CYP2C19 or CYP2D6, and they are therefore unlikely to interact with cimetidine.

Psychotropic drugs

The drug interactions between AEDs and psychotropic agents focus on the cytochrome P450 system. For example, the enzyme-inducing AEDs PB, PHT and CBZ stimulate the metabolism of TCAs, and TCAs have an inhibitory effect on the metabolism of some AEDs[67], resulting in a reduction in the plasma concentration of TCAs, with a concomitant increase in the plasma concentration of coadministered AEDs. Example of TCAs that interact in this complex manner include nortryptiline, imipramine, nomifensine, and trazodone.

The newer antidepressants that inhibit serotonin reuptake, for example fluoxetine (Prozac®), inhibit the isoenzyme CYP3A4, CYP2D6, CYP2C19 and may result in the elevation of plasma concentrations of CBZ and PHT.[68] When CBZ is coadministered with fluoxetine, it should be inhibited at the lower end of the therapeutic dose range to allow the increase in plasma concentration, while reducing the risk of toxicity. If fluoxetine is to be added to patient's drug regimen, which already comprises CBZ, the CBZ dosage adjustment should be guided by CBZ plasma drug concentration monitoring. This advice also applies to PHT. Sertraline, a 5HT-reuptake inhibitor that is indicated for the treatment of depression and anxiety, when coadministered with LTG can lead to LTG toxicity which result from the inhibition of glucuronidation of LTG by inhibition of UGT isoenzymes.

Many of the anxiolytic BZDs are metabolised by CYP3A4, and their metabolism may be altered by concomitant adminitration with AEDs, the result depending on whether the CYP isoenzyme is induced or inhibited.[69] For example, CBZ and PHT, both potent inducers of CYP3A4, decrease the plasma concentration of midazolam (MDZ), whereas VPA increases the plasma concentration of lorazepam (LZP) by inhibiting UGT activity.[70]

Haloperidol, used for the treatment of schizophrenia and mania, is metabolised by CYP2D6 and in part by CYP3A. Hence, the plasma concentration of haloperidol may be reduced if it is coadministered with a CYP3A isoenzyme-inducing AED. Monitoring of plasma concentration of concomitantly administered AEDs and psychotropic drugs may be useful in preventing any adverse consequences of drug interactions.

Antifungal agents

Fluconazole is indicated for the treatment of fungal infections, for example, genital candidiasis, and it is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol. Fluconazole is an inhibitor of the cytochrome P450 isoenzymes CYP2C9 and CYP2C19, the principal metabolizing enzymes for PHT.[66] The coadministration of fluconazole and PHT can be expected to be associated with a clinically significant increase in PHT plasma concentrations, and these may require the adjustment to maintain safe therapeutic concentrations.[71] Most of the second-generation AEDs, such as VGB, LTG, TGB, LEV, OXC, ZNS, and GBP, are not substrates of either CYP2C9 or CYP2C19 and are therefore unlikely to interact with fluconazole.

Antibiotics

Erythromycin is indicated for the treatment of erythromycin-sensitive bacteria. It is used in a wide range of clinical infections including tonsillitis, secondary infections in influenza, eye infections, pre- and post- operative prophylaxis, and genitourinary infections. Erythromycin is an inhibitor of CYP3A4, therefore coadministration with CBZ may lead to an increase in plasma concentrations of CBZ. Patients should be closely monitored and the CBZ dosage should be adjusted if necessary. Two studies of healthy volunteers demonstrated that the second-generation AEDs, OXC and TGB, are not affected by coadministration with erythromycin.[72]

Clarithromycin is indicated for the treatment of susceptible microorganisms causing infections of the respiratory tract, skin, and soft-tissue infections. In addition, clarithromycin is used for the treatment of *Helicobacter pylori* infections in patients with duodenal ulcers. Clarithromycin is both a substrate and an inhibitor of CYP3A, so it has the potential to reduce the metabolism of drugs that are metabolized by CYP3A. For example, clarithromycin increases the plasma concentration of CBZ, and coadministration of these drugs should be monitored very carefully to avoid CBZ toxicity. The use of second-generation AEDs that are not substrated for CYP3A, such as GBP, LEV, LTG, OXC, and VGB, in combination with clarithromycin may be less problematic.

Antiviral agents

Seizures may occur in about 11% of patients with human immunodeficiency virus (HIV), compared with 1-2% of the general population.[73] Coadministration of antiviral agents and AEDs is very likely in HIV-infected patients, and there is the potential for these agents to interact in number of ways. The wide range of both antiviral agents and AEDs means that the number of potential drug interactions is considerable. Romanilli et al. provided an overview of the potential drug interactions should be considered by any physicians treating HIV-infected patients that required AED therapy.[74] Many of the antiviral agents, such as nevirapine, indinavir, ritonavir, and saquinavir, are metabolized by CYP3A4, which is readily induced by CBZ, PHT, and PB. Concomitant administration of a combination of these agents is likely to lead to insufficient plasma concentrations of the antiviral agent, resulting in increase viral replication and the development of resistance. The dose of the antiviral drug may need to be adjusted upward, although this therapeutic adjustment/intervention has not been tested in clinical studies.[74] Consequently, it may be advantageous to use one of the second-generation AEDs that do not affect CYP3A4, such as GBP, LTG, LEV, or VGB, in combination with antiviral agents.

Cyclosporine

Cyclosporine, which is used as an immunosuppressant, is metabolized by CYP3A. Hence, enzyme inducing AEDs, such as CBZ, PB, and PHT may reduce the plasma concentration of coadministered cyclosporine. Patients required cyclosporine are best treated for their epilepsy with one or more of the second-generation AEDs that are known not to induce CYP3A (e.g., GBP, LTG, LEV, TGB, or VGB). As OXC, which induces CYP3A4 and CYP3A5, may reduce plasma levels of cyclosporine, its use should be avoided in patients requiring immunosuppression with cyclosporine.[75]

Anticancer agents

Anticancer agents generally have a very narrow therapeutic index, they have the potential for lethal side effects, and they are often given at dose that are very close to toxic levels. Hence, any increase in the therapeutic activity as a result of a drug interaction may lead rapidly to the patient experiencing toxicity and adverse side effects. Subtle reductions in activity may reduce efficacy of anticancer agents and lead to a poorer prognosis in terms of a cure for the patient. Cytochrome P450 isoenzymes such as CYP3A are important in the metabolism of anticancer agents (e.g., etoposide, cyclophosphamide, and paclitaxel), and drug interactions with these enzymes may play an important role in anticancer drug safety and efficacy. PB and PHT are observed to enhance the clearance of these drugs be up to threefold.[76] Oncologists should be aware of the potential for adverse drug interactions in patients that already be receiving AEDs for their epilepsy or in patients who are prescribed AEDs to minimize cancer- and anticancer agent-induced seizures. There is no data reporting how the second-generation AEDs affect anticancer agents. In theory, those AEDs that do not undergo metabolism of interfere with cytochrome P450 isoenzymes should not interact with the anticancer agents currently in use, and should be the preferred treatment option in such patients.

IX. Quality of life (QOL) in Epilepsy

QOL is a subjective concept. From the patient's perspective, it refers to how patient feels and functions. Medicine, however, focuses intensely on medical outcome in its examination of symptoms, signs, and laboratory studies as defined from the doctor's perspective. Although interviews with the patient have always been an integral part of how doctor assess decrease state and effects of therapy, the patient's view has taken a backseat to the doctor's.

One might argue that the patient is biased, unfamiliar with medical terminology, untrained in making medical observations, unable to separate social from medication effects from underlying disease processes, and capable of reporting information that is heavily contaminated by expectation and desire. Therefore, the patient's perspective is useful only when such elements are filtered out by the doctor's professional objectivity. The patient is the only one who knows how he or she feels, how the disorder affects self-confidence, ability to socialize, obtain work, and function at home and on the job. Surely, the patient's reports may be biased, as may the doctor's. However, the patient is the person who must define his own QOL. Only the patient can evaluate QOL and relate it to his own expectations. Only the patient knows if an imbalance exists between expectation and reality. The balance between perceived and desired status is the essence of QOL.

Epilepsy, like many other chronic conditions, is characterized by uncertainly. Its severity and prognosis are variable, and seizure, its outward manifestation, are unpredictable. Some chronic conditions are also stigmatizing, and epilepsy, for reasons rooted deep in its history. Because of its clinical uncertainty and its social meaning, the impact of epilepsy on a person's QOL can be significant.[13]

The need for a measure to assess quality of life in epilepsy has been apparent for some time. Although generic measure is available, none covers all of the many critical epilepsy-specific topics. Participants at a workshop sponsored by the International League Against Epilepsy held in Porto, Portugal, in 1992, determined that QOL measure for epilepsy can fill an important need for assessing the general epilepsy population.[14] At the American Epilepsy Society annual meeting in December 1992, the Quality-of-Life in Epilepsy (QOLIE) Development Group has reported on its work in developing such as a measure, the QOLIE inventory. The goal of the symposium was to increase awareness among health care professionals of the importance the QOL concept has for persons with epilepsy.[77]

Health-related quality of life (HRQOL) measures, which assess daily functioning and well-being, can complement traditional outcomes and help to capture the full range of relevant clinical endpoints. The QOLIE-89 is a HRQOL measure for people with epilepsy that includes the SF-36 as the generic core and plus disease-targeted items.[77]

Auravan Sinraprakit, studied QOL in epilepsy in Thailand, Nov 1997 to Jun 1998 with Health public support, and created a questionnaire which was developed from Baker.[78,79] Providing support for structual and content validity and reliability, it covered aspects of seizure severity, life fulfillment scale, adverse drug events, master and affect balance. Her study concluded that the developed questionnaire can be applied to measure QOL in Thai epileptic patients. Unfortunately, length of content in questionnaire is an obstruction to complete the intensive. In order to solve this problem, we will evaluate only adverse drug events, global health (SF-12) and psychosocial aspects, as an indicator for QOL in epilepsy by comparing before and after DIMs. Psychosocial questionnaire has been created by Chaplin[80], composed of 42 questions which weighed score according to Table 2.5.

Table 2.5 Psychosocial questionnaire[78]

Aspects	Questionnaire number	Weighting
Attitude towards accepting the seizures	1	2.424
	15	5.076
	29	2.500
Fear of having seizures	2	1.719
	16	6.016
	30	2.666
Fear of stigma in employment	3	2.326
	17	5.504
	31	2.171
Lack of confidence about the future	4	3.387
	18	3.79
	32	2.823
Lack of confidence about traveling	5	4.961
	19	2.283
	33	2.756
Adverse reaction on social life	6	2.481
	20	3.953
	34	3.566
Adverse reaction on leisure	7	3.651
	21	3.953
	35	3.566
Change of outlook on life/self	8	4.094
	22	2.126
	36	3.78

Table 2.6 (continued) Psychosocial questionnaire[78]

Aspects	Questionnaire number	Weighting
Difficulty communicating with the family	9	2.705
	23	4.098
	37	3.197
Problems with taking medication	10	3.033
	24	4.344
	38	2.623
Distrust of the medical profession	11	3.643
	25	2.248
	39	4.109
Depression or emotional reactions	12	3.71
	26	3.548
	40	4.109
Feelings of increased social isolation	13	2.276
	27	5.772
	41	1.951
Lethargy / lack of energy	14	2.773
	28	4.958
	42	2.269

CHAPTER III

MATERIALS AND METHODS

This study was conducted at the epilepsy clinic of Neurological Institute in Bangkok from June 2002 to March 2003. The ethical review committee on human research, Neurological Institute, approved the study protocol on 23rd May, 2002.

MATERIALS

1. Material and collecting data
   - Drug interaction monitoring form (Appendix I)
   - Adverse events of AEDs form (Appendix II)
   - SF – 12 (Appendix III)
   - Psychosocial questionnaire (Appendix IV)
2. Literature
   - Tatro DS. Drug interaction Fact™. Missouri: Facts and comparison; 2002[81]
   - Relevant articles of DIs from various standard journals
3. Instruments and material used for detecting blood levels of carbamazepine, clonazepam, phenytoin, phenobarbital and sodium valproate (Appendix VII).

I. Definitions

A. DIs

The term DIs come to denote the phenomenon of "two of more drugs or substances interacting in such a manner that the effectiveness or toxicity of one or more of the drugs is altered". While some outcomes of DIs are beneficial, for example co-administration of amoxycillin and clavulanic acid, others are clinically harmful.[82] This thesis will focus on D-DIs that lead to adverse events in patients.

A DI pair typically consists of "object drug" and "precipitant drug". The object drug is the drug whose action is altered by the interaction and the precipitant drug is the drug that causes the altered action of the object drug .

- Object drug is the drug whose action is altered by the interaction.
- Precipitant drug is the drug that caused the altered action of the object drug.
- Possible DI is DI predicted from the pharmacodynamic or pharmocokinetic basis of interacting drug which is documented in standard references but is not actually occurred in patient.
- Actual DI is DI actually occurred in patient and is confirmed by clinical signs and symptoms, laboratory data, physician opinion and information documented in standard reference.

B. Severity

Severity of the interaction in this study is based on the definition of Tatro DS.[81] The degree of severity has been divided into three levels which are defined as :-

Minor :The effects are usually mild; consequences may be bothersome or unnoticeable, but should not significantly affect the therapeutic outcome. Additional treatment is usually not required.

Moderate :The effects may cause a deterioration in a patient's clinical status. Additional treatment, hospitalization or extension of hospital stay may be necessary.

Major :The effects are potentially life-threatening or capable of causing permanent damage.

C. AEDs

AEDs in this study includes drugs list; carbamazepine, clonazepam, phenytoin, phenobarbital, topiramate, lamotrigine, oxcarbamazepine, sodium valproate and gabapentin.

D. QOL

QOL includes QOL in aspects of general health, adverse drug events and psychosocial aspect. In this study, SF – 12, adverse events of AEDs form and psychosocial questionnaire will be used to evaluate QOL.

II. Sample size

Number of patients included in this study was determined from potential DIs incidence from preliminary study[83] by the following equation[84]

$$n = (Z_{\alpha}^{2} pq) / d^{2}$$

Where

n = sample size

Z_{α} = Z- statistics for confidence which is 95% or α= 0.05, thus the value of Z_{α} is equal to 1.96

p = incidence of potential DIs determined from the preliminary study which was 52.2% or 0.52 [83]

q = 1 – p = 1 – 0.52 = 0.48

d = error in the study, defined as 10% of p (0.1 x p)

According, calculated sample size was equal to 310, or the sample size needed for the study was at least 310 patients. Percentage of drop – out in this study was limited in 10%, so the sample size needed for the study was 341 patients.

II. Subjects

Inclusion criteria Patients with the following characteristics are included into the study:

1. Patients are identified as epilepsy patients by neurologists and sign in consent forms
2. Patients register to be outpatients in epileptic clinic with the age of at least 18 years
3. Taken AEDs or AED(s) with other prescribed drug(s)
4. Patients must take the medications regularly and recognition how to act when missing the doses
5. Patients must be able to complete Health related Quality of Life (HRQOL) questionnairs by researcher interview

Exclusion criteria Patients with the following characteristics are excluded from this study:

1. Patients with history of hepatic or renal impairment, alcoholism
2. Patients taken medication by tube feeding

III. Methods

A. Data collection

Patients' background information related to the study from medical records were obtained by pharmacist including demographic data, past medical history, social history, family history, drug allergy, frequency of epilepsy, symptom and type of epilepsy. Questionnaires of HRQOL in aspects of general health (SF – 12), adverse events of AEDs and psychosocial were recorded.[78] Patients were interviewed by pharmacist and assistants and educated to recorded epilepsy diary (Appendix V). Epilepsy diary was contained the list of administered drugs, abnormal symptoms during home stay, seizure provoke and adverse events.

Questionnaires of HRQOL, originally in English, were translated into Thai and back translated then applied to 129 epileptic patients.[78] The validity and reliability tests were performed. The study of Orawan Silpakit showed that this instrument was valid and reliable to measure QOL in Thai epileptic patients.[78]

In this study, HRQOL was concerned in 3 parts as following:

- The questionnaire of SF – 12, is composed of 11 questions and associates with general health of patients. The range of scores varies from 12 to 51, positively correlation.
- The questionnaire of adverse events of AEDs, is composed of 19 questions. The range of scores varies from 0 to 38, negatively correlation.
- The questionnaire of psychosocial, is composed of 14 domains from 42 questions. Each domain is generated from 3 questions which difference weigth (Table 2.4). The range of scores in each domain varies from 0 to 20, negatively correlation.

HRQOL, SF – 12, adverse events of AEDs and psychosocial questionnaires were recorded at steady state of all taken drugs at least 2 weeks. The period between two assessments performed at least one month apart but no longer than 3 months. If duration between two assessments was longer than 3 months, these patients were drop – out.

- In patient presented without DI (NDI), the first and second QOL assessment were performed at first meeting and second meeting, at least 2 weeks apart, but no longer than 3 months.
- In patient presented with possible DI (PDI), the first QOL assessment were performed at first meeting and the second assessment were performed after drug interaction monitoring (DIM) at least 2 weeks apart, but no longer than 3 months.
- In patient presented with actual DI (ADI), the first QOL assessment were performed at first meeting and the second assessment were performed after drug interaction monitoring (DIM) and ADI was disappeared. In case which dosage, duration, and/or new drug(s) were assigned, the second assessment was performed at a new steady state, at least 4-5 half-life of drug.

B. Patients evaluation

Patients were evaluated and educated by pharmacist how to take medicine and how to act when missing the dose. All subjects were trained to record epilepsy diary (Appendix V).

C. Drug interaction identifications

Pharmacist identify DIs occurrence and confirm with standard journals. Primarily, patients are classified into three groups following: 1) NDIs 2) PDIs and 3) ADIs

D. Procedure for DIM

1. Pharmacist and neurologist worked together at epilepsy clinic to screen patients and to detect clinical signs and symptoms, target parameters which related to DIs.
2. Patients are classified into three groups; NDI, PDI and ADI
3. Pharmacist monitored DIs when patients visited at epilepsy clinic. Also, the spontaneous record in epilepsy diary was applied to detect DIs.
   - Group of NDIs
     - DIMs were performed when medications were changed
   - Group of PDIs
     - DDI(s) was identified by pharmacist, based on information from standard reference.
     - Result of DDI(s) was predicted and target parameter was determined.
     - Patients' clinical sings and symptoms including laboratory results or objective data particularly those associated with object drug were monitored and recorded in DIM form.
   - Group of ADIs
     - Identify potentially interacting drug and review standard reference to support ADIs.
     - Patients' clinical sings and symptoms including laboratory results or objective data particularly those associated with object drug were monitored and recorded in DIM form.
     - Use alternative non – interacting medications or adjust dosage or dosing time to avoid ADIs
     - Monitor the same parameter to confirm DI disappearance.

In this study, routine blood levels of drugs monitoring in Neurological Institute, clinical sings and symptoms and other objective data were applied to confirm DIs occurrence.

In cases of an oral contraceptive (OC) and AED(s) interaction, it will be considered as DIs if breakthrough is detected at least 2 times per months for 3 months during coadministration of OC and AED(s), and disappear after discontinuation of OC or use of non – interacting drug.

In cases of antidepressant or antianxiety and AED(s) interaction, it will be considered as DI if score determined by Hamilton rating scale for depression or anxiety (Thai version) (Appendix VI) was increased from baseline more than 50 percentage. Hamilton rating scale was recorded by researcher interview. Each patient who taken this combined drugs was determined 2 times and at least 1 month apart.

In case of antihistamine or sedative/hypnotic and AED(s) interaction, it will be considered as DIs if visual analog scale (Appendix VI) of second assessment was higher than baseline more than 50 percentage. Visual analog scale was recorded by epileptic patients. Each patient who taken this combined drugs was determined 2 times and at least 1 month apart.

In case of antihypertensive and AED(s) interaction, it will be considered as DIs if failure of control blood pressure is detected at optimal dose. And discontinuation of object drug or use of non – interacting drug, blood pressure was in control. Blood level was recorded at least 2 times per month for at least a month.

In case interacts between drug that decrease seizure threshold and AEDs, it will be considered as DIs if frequency and/or duration of seizure was increased from baseline more than 50 percentage. However, neurologist participate to conclude DI for rule out pathology confounding.

E. Data analysis and statistical

- Descriptive analysis is used to described demographic characters of subjects and determine prevalence of DI

$$\text{Prevalence of total DIs} = \frac{\text{Number of patients with possible DIs + Actual DIs}}{\text{Total patients}}$$

$$\text{Prevalence of Possible DIs} = \frac{\text{Number of patients with Possible DIs}}{\text{Total patients}}$$

$$\text{Prevalence of Actual DIs} = \frac{\text{Number of patients with Actual DIs}}{\text{Total patients}}$$

- t-test analysis is performed to evaluate relationship between DIs and number of medications taken in epileptic. Significant level are set at $p\text{-value} < 0.05$
- Pair t - test analysis is performed to compare mean score of adverse events of AEDs and quality of life between before and after drug interaction monitoring. Significant level are set at $p\text{-value} < 0.05$

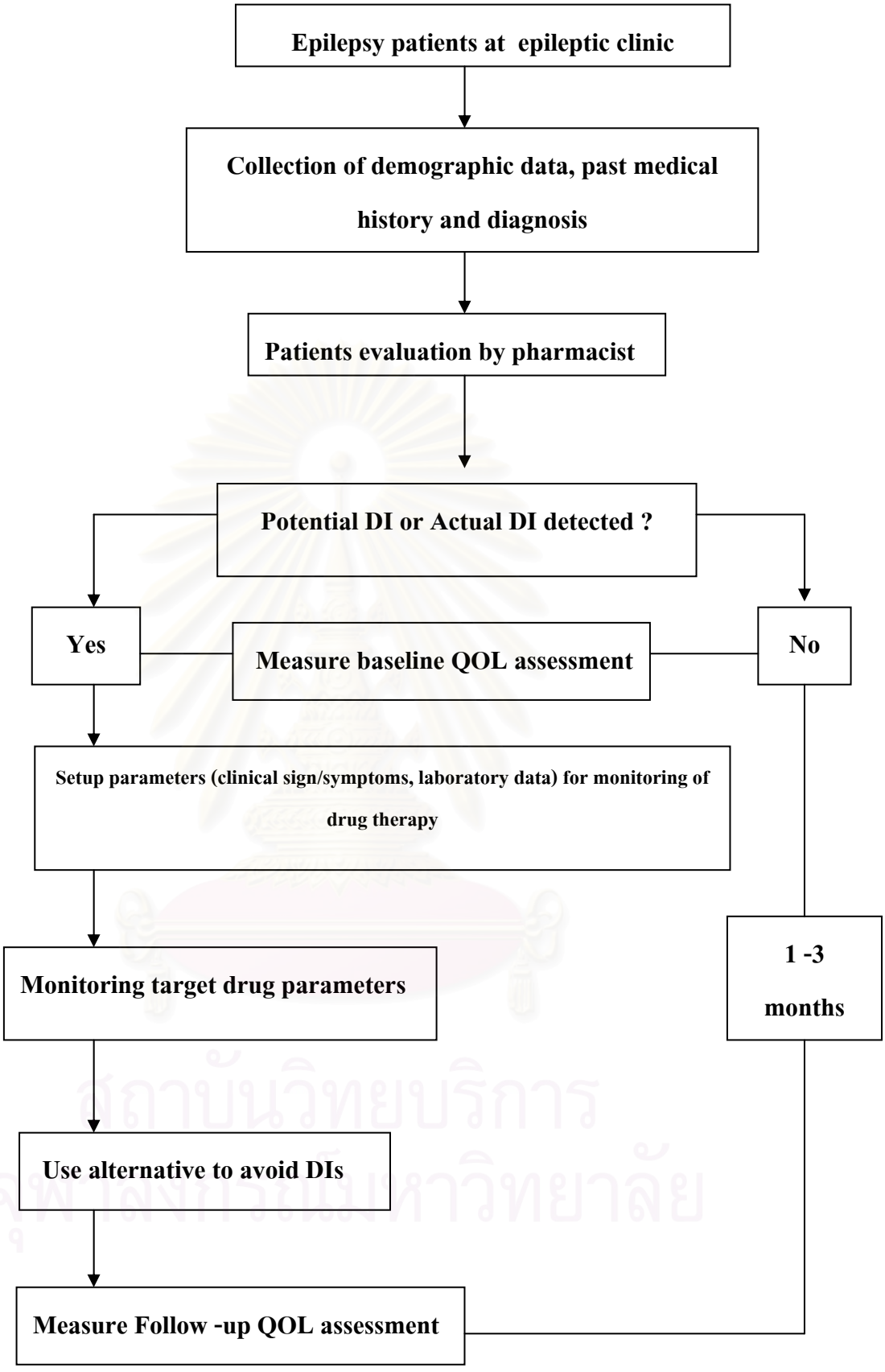


Figure 3.1 Protocol for Drug interaction monitoring

CHAPTER IV

RESULTS

This study was performed to prospectively assess the magnitude of DIs during ten - month period (1st of June 2002 to 31st of March 2003). According to inclusive criteria, 312 of epileptic patients were enrolled, 148 cases (47.4%) were male and 164 cases (52.6%) were female, ranging in aged between 18 to 68 (mean=39.4, SD=11.7). Majority of sample was single status (156 cases, 50.0%), graduated in primary or high school (215 cases, 69.0%), routine employment (167 cases, 53.5%). About 47 cases (15.1%) and 28 cases (9.0%) have drinking and smoking habits, respectively. Demographic feature of all epilepsy patients was shown in Table 4.1

In aspect of clinical characteristics, mostly, 147 cases (47.1%) of epilepsy patients were generalized seizure, 248 cases (79.5%) of epilepsy etiology were cryptogenic, and 164 cases (52.6%) presented frequency of seizure at least 1 times but less than 12 times per year. Table 4.2 depicted clinical characteristics of all epileptic patients.

Table 4.1 Demographic characteristic of epilepsy patients classified by type of Drug Interactions

Demographic characteristics	All patients (312 cases)	NDIs* (225 cases) n (%)	PDIs** (82 cases) n (%)	ADIs*** (5 cases) n (%)
Gender				
Male	148 (47.4)	105 (46.7)	43 (52.4)	-
Female	164 (25.6)	120 (53.3)	39 (47.6)	5 (100)
Age, years (Mean ± SD)	39.4±11.7	38.5± 11.6	42.7± 11.2	44.7± 14.1
Status				
Single	156 (50.0)	117 (52.0)	38 (46.3)	1 (20.0)
Married	132 (42.3)	90 (40.0)	38 (46.3)	4 (80.0)
Other	24 (7.7)	18 (8.0)	6 (7.4)	-
Education				
Drop – out	2 (0.6)	1 (0.4)	1 (1.2)	-
Primary to High school	215 (69.0)	159 (70.7)	53 (64.6)	3 (60.0)
Certificate	73 (23.4)	54 (24.0)	18 (22.0)	1 (20.0)
Bachelor degree or higher	22 (7.0)	11 (4.9)	10 (12.2)	1 (20.0)
Employment				
Unemployed	118 (37.8)	78 (34.7)	40 (48.8)	-
Routine employed	167 (53.5)	128 (56.9)	35 (42.7)	4 (80.0)
Occasional employed	27 (8.7)	19 (8.4)	7 (8.5)	1 (20.0)
Drinking	47 (15.1)	39 (17.3)	8 (9.8)	-
Smoking	28 (9.0)	24 (10.7)	4 (4.9)	-

* : patient presented without drug interaction

** : patient presented with possible drug interaction

*** : patient presented with actual drug interaction

Table 4.2 Clinical characteristic of epilepsy patients classified by type of Drug Interactions

Clinical characteristics	All patients (312 cases)	NDIs* (225 cases) n (%)	PDIs** (82 cases) n (%)	ADIs*** (5 cases) n (%)
Age onset of epilepsy, years (Mean ± SD)	18.7±12.5	18.6±12.3	19.0±15.0	24.2±14.6
Duration of epilepsy , years (Mean ± SD)	20.7±12	20±11.5	24.8±14.8	13.0±13.9
Seizure type				
❑ Focal	10 (3.2)	5 (2.2)	5 (6.2)	-
❑ Focal turn to 2 nd GTC****	32 (10.3)	25 (11.1)	7 (8.5)	-
❑ Complex partial	96 (30.8)	72 (32.0)	21 (25.6)	3 (60.0)
❑ Generalized	147 (47.1)	104 (46.2)	42 (51.2)	1 (20.0)
❑ Specific syndrome	2 (0.6)	-	1 (1.2)	1 (20.0)
❑ Other or unclassified	25 (8.0)	19 (8.5)	6 (7.3)	-
Epilepsy etiology				
❑ Idiopathic	13 (4.2)	10 (4.4)	2 (2.4)	1 (20.0)
❑ Cryptogenic	248 (79.5)	179 (79.6)	66 (80.5)	3 (60.0)
❑ Symptomatic	51 (16.3)	36 (16.0)	14 (17.1)	1 (20.0)
Frequency of seizure in past a year				
❑ No seizure	86 (27.6)	72 (32.0)	14 (17.1)	-
❑ At least 1 time and less than 12 times per year	164 (52.6)	106 (47.1)	54 (65.9)	4 (80.0)
❑ At least 1 time per month or more than 12 times per year	42 (13.5)	30 (13.3)	12 (14.6)	-

Table 4.2 (continued) Clinical characteristic of epilepsy patients classified by type of Drug Interactions

Clinical characteristics	All patients (312 cases)	NDIs* (225 cases) n (%)	PDIs** (82 cases) n (%)	ADIs*** (5 cases) n (%)
Frequency of seizure in past a year (continued)				
❑ At least 1 time per week or more than 14 times per month	16 (5.1)	14 (6.2)	1 (1.2)	1 (20.0)
❑ At least 1 time per day or more than 7 times per week	4 (1.3)	3 (1.3)	1 (1.2)	-

* : patient presented without drug interaction

** : patient presented with possible drug interaction

*** : patient presented with actual drug interaction

****: general tonic clonic seizure

Figure 4.1 Seizure types and number of patients presented with NDI, PDI and ADI

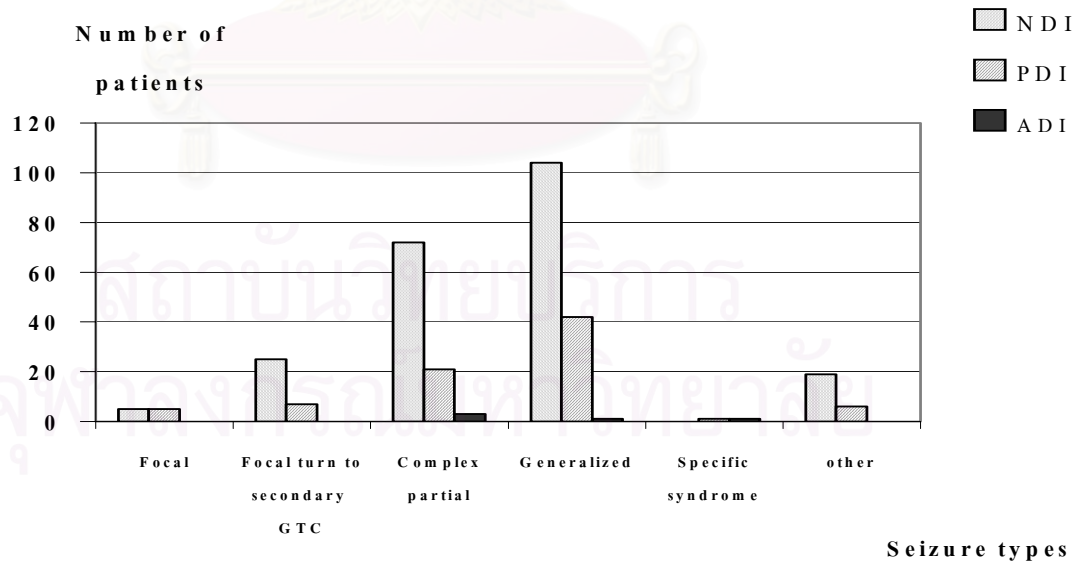
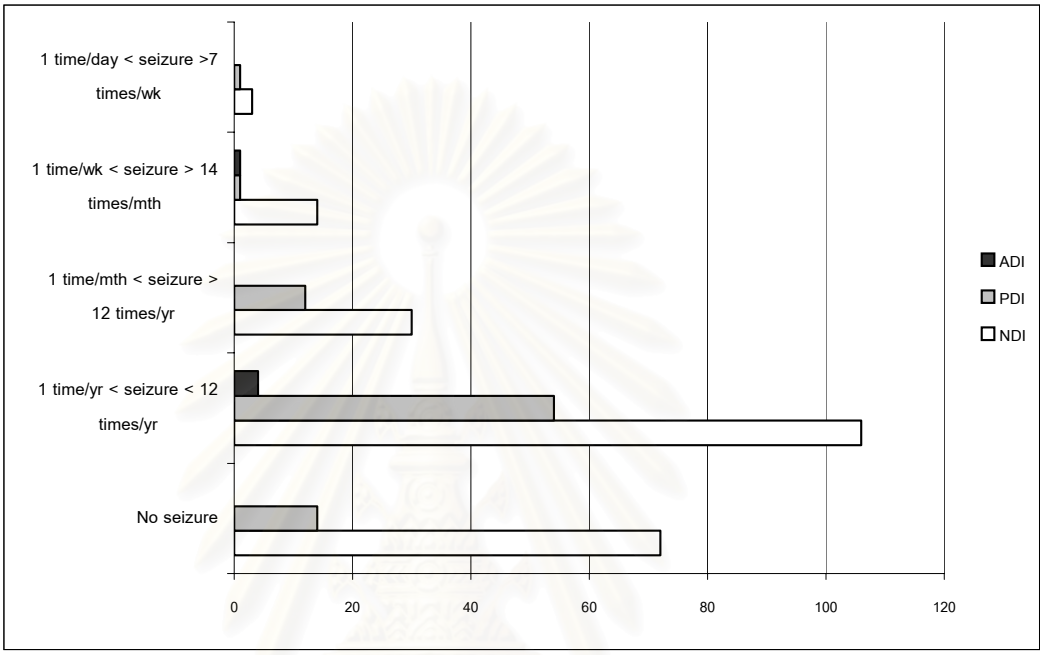


Figure 4.2 Seizure frequency and number of patients presented with NDI, PDI and ADI



An average number of medication prescribed to this sample was 3.61 medications (SD = 1.32). After DIM, these patients were classified into three groups,

1). NDIs 225 cases (72.12%) administered average 3.17 medications (SD = 1.06)

2). PDIs 82 cases (26.28%) administered average 4.74 medications (SD = 1.36)

3). ADIs 5 cases (1.60%) administered average 4.00 medications (SD = 0.71)

The distribution of number of medications and patients presented with and without DIs was shown to Table 4.3

Analysis of varience (ANOVA) used to test differences of medication in average among the three groups of patients, it was found that the average number of medication among the three groups was significantly difference ($p < 0.001$) (Table 4.4). Multiple comparison made by Least – Significant Different (LSD) test found that only average number of medication in cases presented with NDIs and PDIs was significantly difference ($p < 0.001$).

Table 4.3 Number medications prescribed to epilepsy patients classified by type of DIs

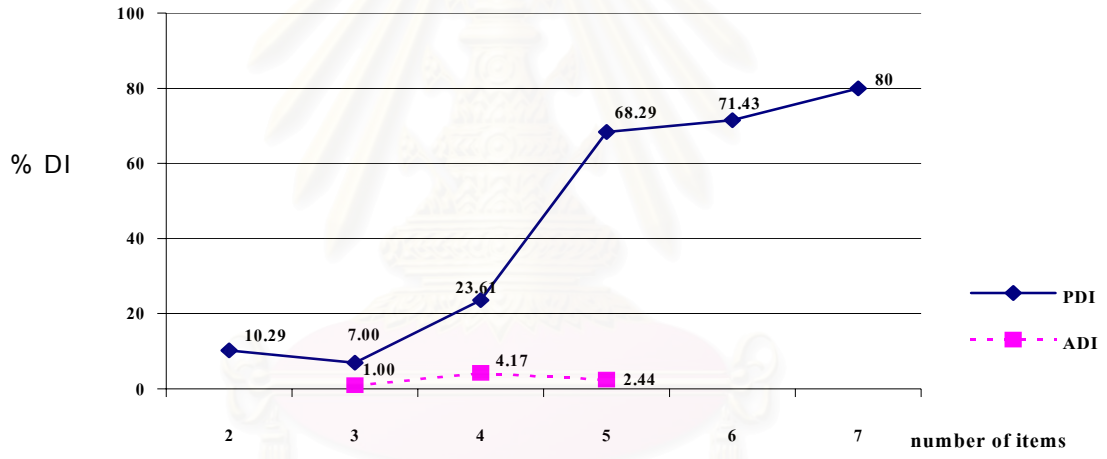
Number of Medications	All patients (312 cases)	NDIs* (225 cases) n (%)	PDIs** (82 cases) n (%)	ADIs*** (5 cases) n (%)
2	68	61 (89.71)	7 (10.29)	-
3	100	92 (92.00)	7 (7.00)	1 (1.00)
4	72	52 (72.22)	17 (23.61)	3 (4.17)
5	41	12 (29.27)	28 (68.29)	1 (2.44)
6	21	6 (28.57)	15 (71.43)	-
7	10	2 (20.00)	8 (80.00)	-

Table 4.4 Distribution of medications between type of DIs

Group of DIs	Distribution of medications			F
	Minimum	Maximum	Mean ± SD	
1. NDIs	2	7	3.17 ± 1.06	57.729 *
2. PDIs	2	7	4.74 ± 1.36	
3. ADIs	3	5	4.00 ± 0.71	

(*:significant at level of 0.001)

Figure 4.3 Correlation between prevalence of DI and number of medications



Before DIMs, 312 prescriptions were enrolled, AEDs which favorable prescribed was PB (203 prescriptions, 65.06%), PHT (196 prescriptions, 62.82%) and CBZ (130 prescriptions, 41.67%), respectively. Drug groups combined with AEDs were classified into 30 groups, shown in Table 4.5. Antianemic drug, folic acid (199

prescriptions, 63.78%), was mostly prescribed with AEDs following by vitamin & minerals (38 prescriptions, 12.18%), DZPs (26 prescriptions, 8.33%), and amitriptyline (20 prescriptions, 6.41%).

After DIMs, group of NDIs, AEDs which favorable prescribed was PB (153 prescriptions, 68.00%), PHT (144 prescriptions, 64.00%) and CBZ (78 prescriptions, 34.67%), respectively. Antianemic drug, folic acid (164 prescriptions, 72.89%), was mostly prescribed with AEDs following by vitamin & minerals (18 prescriptions, 8.00%), muscle relaxants (7 prescriptions, 3.11%), and beta blocker, atenolol (6 prescriptions, 2.67%).

Group of PDIs, AEDs which favorable prescribed was PHT (50 prescriptions, 60.98%), PB (48 prescriptions, 58.54%), and CBZ (28 prescriptions, 34.15%), respectively. Antianemic drug, folic acid (31 prescriptions, 37.80%) was mostly prescribed with AEDs following by DZPs (22 prescriptions, 26.83%), amitiptyline (19 prescriptions, 23.17%) and vitamin & minerals (20 prescriptions, 24.39%), respectively.

Group of ADIs, AEDs which the most favorable prescribed was CBZ (3 prescriptions, 60.00%). Antianemic drug, folic acid, was mostly prescribed with AEDs (4 prescriptions, 80.00%) following by hormones (3 prescriptions, 60.00%). Table 4.5 showed drug groups that prescribed in epilepsy patients classified by type of DIs.

Table 4.5 Drug groups prescribed in epilepsy patients classified by type of DIs

Drug group	Group of DI (%)			Total
	NDIs (225 cases)	PDIs (82 cases)	ADIs (5 cases)	prescriptions (%) (312 cases)
1. Anticonvulsants				
❑ PB	153 (68.00)	48 (58.54)	2 (40.00)	203 (65.06)
❑ PHT	144 (64.00)	50 (60.98)	2 (40.00)	196 (62.82)
❑ CBZ	78 (34.67)	28 (34.15)	3 (60.00)	130 (41.67)
❑ VPA	40 (17.78)	14 (17.07)	2 (40.00)	56 (17.95)
❑ CZP	31 (13.78)	10 (12.20)	-	41 (13.14)
❑ TPM	12 (5.33)	3 (3.66)	-	15 (4.81)
❑ GBP	1 (0.44)	2 (2.44)	-	3 (0.96)
❑ LMG	1 (0.44)	1 (1.22)	-	2 (0.64)
2. Antianemics				
❑ Folic acid	164 (72.89)	31 (37.80)	4 (80.00)	199 (63.78)
3. BZPs				
❑ DZP	4 (1.78)	22 (26.83)	-	26 (8.33)
❑ Alprazolam	-	6 (7.32)	-	6 (1.92)
❑ Clobazam	4 (1.78)	2 (2.44)	-	6 (1.92)
❑ Lorazepam	-	5 (6.10)	-	5 (1.60)
❑ Clarazepate	-	3 (3.66)	-	3 (0.96)
4. Vitamin & minerals	18 (8.00)	20 (24.39)	-	38 (12.18)
5. TCAs				
❑ Amitriptyline	1 (0.44)	19 (23.17)	-	20 (6.41)
❑ Nortriptyline	-	1 (1.22)	-	1 (0.32)
❑ Imipramine	-	1 (1.22)	-	1 (0.32)

Table 4.5 (continued) Drug groups prescribed in epilepsy patients classified by type of DIs

Drug group	Group of DI (%)			Total
	NDIs (225 cases)	PDIs (82 cases)	ADIs (5 cases)	prescriptions (%) (312 cases)
6. Nonsteroidal anti – inflammatory agents (NSAIDs)				
❑ Aspirin	3 (1.33)	9 (10.98)	-	12 (3.85)
❑ Paracetamol	2 (0.88)	2 (2.44)	-	4 (1.28)
❑ Diclofenac	3 (1.33)	1 (1.22)	-	4 (1.28)
❑ Mefenamic acid	3 (1.33)	-	-	3 (0.96)
❑ Piroxicam	1 (0.44)	1 (1.22)	-	2 (0.64)
❑ Indomethacin	-	1 (1.22)	-	1 (0.32)
❑ Meloxicam	1 (0.44)	4 (4.88)	-	5 (1.60)
7. Beta blockers				
❑ Atenolol	6 (2.67)	9 (10.98)	-	15 (4.81)
❑ Propranolol	1 (0.44)	4 (4.88)	1 (10.00)	5 (1.60)
8. Antacids & Antiulcerants				
❑ Antacids	-	6 (7.32)	-	6 (1.92)
❑ Ranitidine	4 (1.78)	2 (2.44)	-	6 (1.92)
❑ Omeprazole	-	1 (1.22)	-	1 (0.32)
9. Antiflatulants & Laxatives and Purgatives				
❑ Simethicone	1 (0.44)	-	-	1 (0.32)
❑ Psyllium hydrophillic mucilliod	1 (0.44)	-	-	1 (0.32)
❑ Sennosides	1 (0.44)	-	-	1 (0.32)
❑ Mixture of Carminative	1 (0.44)	1 (1.22)	-	2 (0.64)
10. Diuretic				
❑ Hydrochlorothiazide	-	1 (1.22)	-	1 (0.32)

Table 4.5 (continued) Drug groups prescribed in epilepsy patients classified by type of DIs

Drug group	Group of DI (%)			Total
	NDIs	PDIs	ADIs	prescriptions (%)
	(225 cases)	(82 cases)	(5 cases)	(312 cases)
11. Narcotic Analgesics				
❑ Tramadol	-	1 (1.22)	-	1 (0.32)
12. Antidiabetics				
❑ Metformin	2 (0.88)	4 (4.88)	-	6 (1.92)
❑ Glibenclamide	1 (0.44)	1 (1.22)	-	2 (0.64)
❑ Gliclazide	1 (0.44)	-	-	1 (0.32)
❑ Glipizide	-	1 (1.22	-	1 (0.32)
13. Angiotensin converting enzyme inhibitor				
❑ Enalapril	2 (0.88)	1 (1.22	-	3 (0.96)
14. Serotonin reuptake inhibitor				
❑ Fluoxetine	-	1 (1.22)	-	1 (0.32)
15. Calcium Channel Blockers				
❑ Felodipine	-	-	1 (10.00)	1 (0.32)
❑ Manidipine	-	1 (1.22)	-	1 (0.32)
16. Hormones				
❑ Mestranol			2 (20.00)	2 (0.64)
❑ Ethinylestradiol	-	-	1 (10.00)	1 (0.32)
17. Anticoaglulants & Antithrombotics & Fibrinolytics				
❑ Warfarin	-	-	1 (10.00)	1 (0.32)
❑ Ticlopidine	1 (0.44)	-	-	1 (0.32)
❑ Clopidogrel	-	1 (1.22)	-	1 (0.32)

Table 4.5 (continued)Drug groups prescribed in epilepsy patients classified by type of DIs

Drug group	Group of DI (%)			Total
	NDIs (225 cases)	PDIs (82 cases)	ADIs (5 cases)	prescriptions (%) (312 cases)
18. Antipsychotics				
❑ Perphenazine	-	8 (9.76)	-	8 (2.56)
❑ Thioridazine	-	6 (7.32)	-	6 (1.92)
❑ Haloperidol	-	1 (1.22)	-	1 (0.32)
❑ Tianeptine	-	1 (1.22)	-	1 (0.32)
19. Antibiotics				
❑ Acyclovir	-	1 (1.22)	-	1 (0.32)
❑ Ciprofloxacin	-	1 (1.22)	-	1 (0.32)
❑ Penicillins	2 (0.88)	2 (2.44)	-	4 (1.28)
❑ Norfloxacin	2 (0.88)	-	-	2 (0.64)
❑ Roxithromycin	1 (0.44)	1 (1.22)	-	2 (0.64)
20. HMG co – A reductase inhibitors				
❑ Simvastatin	-	5 (6.10)	-	5 (1.60)
❑ Atrovastatin	-	1 (1.22)	-	1 (0.32)
21. Fibric acid				
❑ Gemfibrozil	-	1 (1.22)	-	1 (0.32)
22. Cough & cold remedies				
❑ Triprolidine + pseudoephedrine	1 (0.44)	1 (1.22)	-	2 (0.64)
❑ Bromhexine	-	1 (1.22)	-	1 (0.32)
❑ Dextromethorphan	1 (0.44)	-	-	1 (0.32)

Table 4.5 (continued)Drug groups prescribed in epilepsy patients classified by type of DIs

Drug group	Group of DI (%)			Total
	NDIs (225 cases)	PDIs (82 cases)	ADIs (5 cases)	prescriptions (%) (312 cases)
23. Antihistamines				
❑ Diphenhydramine	-	1 (1.22)	-	1 (0.32)
❑ Chlorpheniramine	2 (0.88)	3 (3.66)	-	5 (1.60)
❑ Brompheniramine	1 (0.44)	-	-	1 (0.32)
❑ Fexofenadine	1 (0.44)	-	-	1 (0.32)
24. Antivertigo				
❑ Dimenhydrinate	1 (0.44)	4 (4.88)	-	5 (1.60)
❑ Betahistine	-	1 (1.22)	-	1 (0.32)
25. Peripheral vasodilator & cerebral activators				
❑ Cinnarizine	-	2 (2.44)	-	2 (0.64)
❑ Flunarizine	2 (0.88)	5 (6.10)	-	7 (2.24)
26. Muscle relaxants				
❑ Paracetamol + orphenadine	7 (3.11)	7 (8.54)	-	14 (4.49)
❑ Baclofen	-	1 (1.22)	-	1 (0.32)
27. Antiparkinsonian				
❑ Levodopa + benserazide	-	1 (1.22)	-	1 (0.32)
❑ Levodopa + carbidopa	1 (0.44)	-	-	1 (0.32)
❑ Selegiline	-	1 (1.22)	-	1 (0.32)
28. Thyroid preparation				
❑ Thyroxin	-	1 (1.22)	-	1 (0.32)
29. Antigout				
❑ Allopurinol	1 (0.44)	1 (1.22)	-	2 (0.64)

Table 4.5 (continued)Drug groups prescribed in epilepsy patients classified by type of DIs

Drug group	Group of DI (%)			Total
	NDIs (225 cases)	PDIs (82 cases)	ADIs (5 cases)	prescriptions (%) (312 cases)
30. Miscellaneous				
❑ Trihexyphenidyl	-	3 (3.66)	-	3 (0.96)
❑ Belladonna + ergotamine	3 (1.33)	-	-	3 (0.96)

Possible pharmacokinetic interactions were determined in PDIs group, 101 events of DDIs, composed of PHT – DZP (15 events, 14.85%), PB – amitriptyline (13 events, 12.87%) and PHT – aspirin (8 events, 7.92%), respectively. Mostly mechanism of potential pharmacokinetic interactions was metabolism process (29 DDIs, 90.63%). Only 2 and 3 events of DDIs occurred in distribution and absorption process. The severity of DIs in 20 DDIs (59 events, 58.42%) was moderate and 12 DDIs (43 events, 42.57%) was minor. Table 4.6 showed possible pharmacokinetic interactions.

Possible pharmacodynamic interactions were determined in PDIs group, 182 events of DDIs, composed of PHT – DZP (15 events, 8.24%), PB – DZP (15 events, 8.24%) and PHT – amitriptyline (15 events, 8.24%). Mostly mechanism of possible pharmacodynamic interactions was additive and combined toxicity (30 DDIs, 51.72%). The severity of all DIs was minor. Table 4.7 showed possible pharmacodynamic interactions.

Table 4. 6 Potential pharmacokinetic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
PHT - DZP	15	2	Metabolism of PHT may inhibit by DZP	May observe PHT toxicity	1,40,81
PB – amitriptyline	13	1	Metabolism of amitriptyline may induce by PB	Serum concentration of amitriptyline may be decreased.	1,40,81
PHT - aspirin	8	1	Aspirin competes with PHT for plasma protein binding.	The pharmacologic and toxic effects of PHT may be increased.	1,40,81
PHT - perfenazine	6	2	Metabolism of PHT may inhibit by perfenazine	May observe PHT toxicity	1,40,81
PB – perfenazine	6	1	Metabolism of perfenazine may enhance by PB	Pharmacologic effects of perfenazine may be reduced. Plasma concentration of PB may be decreased by perfenazine.	1,40,81
PB – thioridazine	5	1	Metabolism of thioridazine may enhance by PB	Pharmacologic effects of thioridazine may be reduced. Plasma concentration of PB may be decreased by thioridazine.	1,40,81
PHT – lorazepam	5	2	Metabolism of PHT may inhibit by lorazepam	May observe PHT toxicity	1,40,81

Table 4. 6 (continued) Potential pharmacokinetic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
CBZ - amitriptyline	4	2	CBZ may induce and competed with amitriptyline for hepatic metabolism.	May observe CBZ toxicity.	1,40,81
PHT - thioridazine	4	2	Metabolism of PHT may inhibit by thioridazine.	May observe PHT toxicity	1,40,81
CBZ - alprazolam	3	2	Metabolism of alprazolam may induce by CBZ	Pharmacological effect of alprazolam may be decreased.	1,40,81
PB - propranolol	3	2	PB increases metabolism and hepatic first – pass extraction of propranolol.	The plasma concentration of propranolol may be decreased.	1,40,81
PHT – allopurinol	3	2	Metabolism of PHT may be inhibited.	May observe PHT toxicity	1,40,81
PHT – alprazolam	3	2	Metabolism of PHT may be inhibited by lorazepam	May observe PHT toxicity	1,40,81
PHT – clorazepate	3	2	Possible alteration of PHT and clorazepate metabolism	Serum PHT concentration may be increased, resulting in an increase the pharmacologic and toxic effects.	1,40,81

Table 4. 6 (continued) Potential pharmacokinetic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
VPA - DZP	3	1	VPA may inhibit metabolism of DZP and displaced DZP metabolites from plasma protein binding sites.	Pharmacokinetic parameters of DZP may be increased: plasma concentration, AUC. Also, sedation may be enhanced.	1,40,81
PHT – antacid	2	1	Antacid decreases rate and extent of absorption of PHT.	AUC and serum concentration of PHT may be reduced.	1,40,81
CBZ - alprazolam	1	2	Alprazolam metabolism may be induced by CBZ.	The pharmacologic effects of alprazolam may be increased.	1,40,81
CBZ - fluoxetine	1	2	Fluoxetine may inhibit metabolism of CBZ.	Toxicity of CBZ may be observed.	1,40,81
PB – haloperidol	1	2	Haloperidol matabolism may be induced by PB.	Serum haloperidol concentration may be decreased.	1,40,81
PB – imipramine	1	2	Metabolism of imipramine may be enhanced.	Lower serum level of imipramine may be observed.	1,40,81

Table 4. 6 (continued) Potential pharmacokinetic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
PB – nortriptyline	1	1	Metabolism of nortriptyline may be induced by PB	Serum concentration of nortriptyline may be decreased.	1,40,81
PHT – chlorpheniramine(CPM)	1	2	PHT may be inhibited the hepatic metabolism by CPM .	Serum PHT concentration may be increased, resulting in an increase in the pharmacologic and toxic effects.	1,40,81
PHT – calcium carbonate	1	1	Calcium carbonate decreases rate and extent of absorption of PHT.	AUC and serum concentration of PHT may be reduced.	1,40,81
PHT – glipizide	1	1	Glipizide may be induced metabolism by PHT.	Higher dose of glipizide for control of hypoglycemia.	1,40,81
PHT – haloperidol	1	2	Haloperidol matabolism may be induced by PHT.	Serum haloperidol concentration may be decreased.	1,40,81
PHT - imipramine	1	2	Metabolism of PHT may be decreased.	May observe PHT toxicity	1,40,81

Table 4. 6 (continued) Potential pharmacokinetic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
PHT – omeprazole	1	2	Omeprazole inhibits the oxidation hepatic of PHT	Serum PHT concentration may be increased, resulting in an increase the pharmacologic and toxic effects.	1,40,81
PHT - simvastatin	1	2	Metabolism of simvastatin may be enhanced.	Plasma concentration of simvastatin may be decreased.	1,40,81
VPA - alprazolam	1	1	VPA may inhibit metabolism of alprazolam and displaced alprazolam metabolites from plasma protein binding sites.	Pharmacokinetic parameters of DZP may be increased: plasma concentration, AUC. Also, sedation may be enhanced.	1,40,81
VPA - antacid	1	1	Antacid increased AUC of VPA.	Bioavailability of VPA increased and may observe VPA toxicity.	1,40,81
VPA - clorazepate	1	1	VPA may inhibit metabolism of clorazepate and displaced metabolites from plasma protein binding sites.	Pharmacokinetic parameters of clorazepate may be increased : plasma concentration, AUC. Also, sedation may be enhanced.	1,40,81

Table 4. 6 (continued) Potential pharmacokinetic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
CBZ – propranolol	1	2	CBZ increases metabolism and hepatic first – pass extraction of propranolol.	The plasma concentration of propranolol may be decreased.	1,40,81

Table 4. 7 Potential pharmacodynamic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
PHT - DZP	15	1	Additive interaction and combined toxicity	Increase CNS depressant effect	1,9,81
PB - DZP	15	1	Additive interaction and combined toxicity	Increase CNS depressant effect	1,9,81
PHT - amitriptyline	15	1	Additive and combined toxicity, and antagonistic interactions	Increase CNS depressant effect and decrease seizure threshold	1,9,81
PB - amitriptyline	13	1	Additive and combined toxicity, and antagonistic interactions	Increase CNS depressant effect and decrease seizure threshold	1,9,81
CBZ - DZP	6	1	Additive interaction and combined toxicity	Increase CNS depressant effect	1,9,81
PB - perphenazine	6	1	Additive and combined toxicity, and antagonistic interactions	Increase CNS depressant effect and decrease seizure threshold	1,9,81
PHT - perphenazine	5	1	Additive and combined toxicity, and antagonistic interactions	Increase CNS depressant effect and decrease seizure threshold	1,9,81

Table 4. 7 (continued) Potential pharmacodynamic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
CBZ - amitriptyline	5	1	Additive and combined toxicity, and antagonistic interactions	Increase CNS depressant effect and decrease seizure threshold	1,9,81
PB – thioridazine	5	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
CBZ - alprazolam	4	1	Additive interaction and combined toxicity	Increase CNS depressant effect	1,9,81
PHT - orphenadrine	4	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PB - orphenadrine	4	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PHT - lorazepam	4	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
CBZ - thioridazine	4	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
PHT - thioridazine	4	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
PHT - flunarizine	4	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PB - flunarizine	4	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
CBZ - perphenazine	3	1	Additive and combined toxicity, and antagonistic interactions	Increase CNS depressant effect and decrease seizure threshold	1,9,81

Table 4. 7 (continued) Potential pharmacodynamic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
PHT - clorazepate	3	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PHT - alprazolam	3	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PB - lorazepam	3	1	Additive interaction and combined toxicity	Increase CNS depressant effect	1,9,81
PB - triprolidine	3	1	Additive interaction and combined toxicity	Increase CNS depressant effect	1,9,81
PHT - baclofen	2	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PB - baclofen	2	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
VPA - perphenazine	2	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
PB - clorazepate	2	1	Additive interaction and combined toxicity	Increase CNS depressant effect	1,9,81
VPA - thioridazine	2	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
PHT - dimenhydrinate	2	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PB - dimenhydrinate	2	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PB - amoxicillin	2	1	Antagonistic interaction	Decrease seizure threshold	1,9,81

Table 4. 7 (continued) Potential pharmacodynamic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
PHT - amoxicillin	2	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
CBZ - amoxicillin	2	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
PB - alprazolam	2	1	Additive interaction and combined toxicity	Increase CNS depressant effect	1,9,81
PB - cinnarizine	2	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PHT - cinnarizine	2	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PB - CPM	2	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
CBZ - clobazam	1	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PHT - clobazam	1	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
CBZ - orphenadrine	1	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PHT - imipramine	1	1	Additive and combined toxicity, and antagonistic interactions	Increase CNS depressant effect and decrease seizure threshold	1,9,81

Table 4. 7 (continued) Potential pharmacodynamic interactions (severity 1=minor, 2=moderate, 3=major)

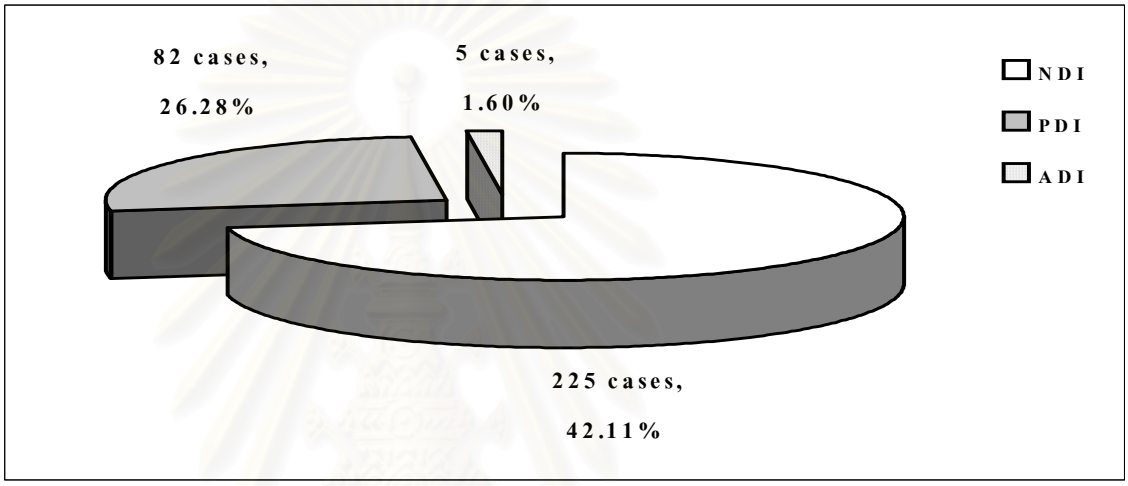
Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
PB - imipramine	1	1	Additive and combined toxicity, and antagonistic interactions	Increase CNS depressant effect and decrease seizure threshold	1,9,81
VPA - imipramine	1	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
TPM - tramadol	1	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
CBZ –tramadol	1	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
TPM - ciprofloxacin	1	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
CBZ - ciprofloxacin	1	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
PB - trifluoperazine	1	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
CBZ - acyclovir	1	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
VPA - amoxicillin	1	1	Antagonistic interaction	Decrease seizure threshold	1,9,81
PB – benadryl	1	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
CBZ - lorazepam	1	1	Additive interaction and combined toxicity	Increase CNS depressant effect	1,9,81
VPA - amitriptyline	1	1	Antagonistic interaction	Decrease seizure threshold	1,9,81

Table 4. 7 (continued) Potential pharmacodynamic interactions (severity 1=minor, 2=moderate, 3=major)

Drug – Drug interactions	No. of events	Severity	Proposed mechanism of interaction	Predicted effect	References
CBZ – triprolidine	1	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PHT - tripolidine	1	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PHT - CPM	1	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
CBZ – CPM	1	1	Additive interaction and combined toxicity	Increase adverse reaction of drowsiness	1,9,81
PB – nortriptyline	1	1	Additive and combined toxicity, and antagonistic interactions	Increase CNS depressant effect and decrease seizure threshold	1,9,81
PHT - nortriptyline	1	1	Additive and combined toxicity, and antagonistic interactions	Increase CNS depressant effect and decrease seizure threshold	1,9,81

All of 312 patients which enrolled in this study, prevalence of PDIs and ADIs were 26.28% (82 cases) and 1.60% (5 cases) respectively. Figure 4.3 depicted prevalence of PDIs and ADIs.

Figure 4.4 Prevalence of NDI, PDI and ADI



In aspect of ADIs (5 cases, 1.60%), taken AEDs with OCs, hormones, and anticoagulant. OCs interacted with AEDs in 3 cases (60.0.%), but hormones (estrogen) and anticoagulant (warfarin) interacted to each one. CBZ (3 cases, 60.00%) and PHT (2 cases, 20.00%) was taken in group of ADIs. Severity of all ADIs was moderate. ADIs were shown in Table 4.8.

Table 4. 8 Actual drug interactions (severity 1 = minor, 2=moderate, 3=major)

Drug – Drug interactions[#]	No. of events	Severity	Duration of drugs combination	Proposed mechanism of interaction	Results of interaction	References
CBZ (400 mg/day) – PB (60 mg/day) - OCs (Anamai®)[1](1 tablet/day)	1	2	3 years	CBZ and PB may increase hepatic metabolism of OCs.	Breakthrough bleeding (2 times of menstruation per month). When OCs was discontinued, menstruation was normal.	1,60,81
PHT (300 mg/day) – OCs (Anamai®)[1](1 tablet/day)	1	2	2 years	PHT may increase hepatic metabolism of OCs.	Same as above	1,60,81
CBZ (500 mg/day) – OCs (Anna®)[2](1 tablet/day)	1	2	1 year	CBZ may increase hepatic metabolism of OCs.	Same as above	1,60,81

(# ; In all cases no other medications bas been taken besides studied drug and AEDs , 1 = norethisterone 1 mg and mestranol 0.05 mg , 2 = levonorgestrel 150 ug and ethinylestradiol 30 ug, 3 = 0.625 mg of conjugated estrogen)

Table 4. 8 (continued) **Actual drug interactions (severity 1 = minor, 2=moderate, 3=major)**

Drug – Drug interactions[#]	No. of events	Severity	Duration of drugs combination	Proposed mechanism of interaction	Results of interaction	References
PHT (200 mg/day) – estrogen replacement therapy (Premarin® 0.625 mg)[3] (1 tablet/day)	1	2	2 months	PHT induction of estrogens hepatic metabolism and sex hormone binding globulin synthesis combine to reduce effective concentrations of estrogens hormones.	Failure of hormone supplement therapy, hot flush was disappeared after changing PHT to VPA.	1,60,81
PHT (300 mg/day) – Warfarin (7.5 mg/day)	1	2	1 month	PHT may initially displace warfarin from protein binding sites followed by enzyme induction increasing metabolism.	INR was 1.26 after combination of 7.5 mg of warfarin and 300 mg of PHT per day for 2 months. After PHT was discharged for 3 months and warfarin dosage was decreased to 5 mg per day, INR went up to 1.97.	1,81

(# ; In all cases no other medications bas been taken besides studied drug and AEDs , 3 = 0.625 mg of conjugated estrogen)

After quality of life assessment, 138 patients were classified into three groups, NDIs (97 cases), PDIs (38 cases) and ADIs (3 cases). In aspect of adverse events of AEDs, mean score baseline was 10.40 (SD =6.24) and follow-up was 9.98 (SD=6.30) in a group of NDIs, mean score baseline was 10.66 (SD =6.70) and follow-up was 10.50 (SD=6.12) in a group of PDIs and mean score baseline was 9.00 (SD=4.58) and follow-up was 9.67 (SD=3.79) in a group of ADIs, respectively. The pair t-test indicated no significant difference between baseline and follow-up mean score in three groups, shown in Table 4.9

Table 4.9 Mean score of adverse events of AEDs in groups of NDIs and DIs

DIs Group	Adverse events Base line scores		Adverse events Follow-up scores		t	df	p - value
	Mean	SD	Mean	SD			
NDIs (97 cases)	10.40	6.24	9.98	6.30	0.611	96	0.542
PDIs (38 cases)	10.66	6.70	10.50	6.12	0.173	37	0.864
ADIs (3 cases)	9.00	4.58	9.67	3.79	-0.329	2	0.774

In aspect of general health (SF – 12), mean score baseline was 37.33 (SD =4.12) and follow-up was 36.07 (SD=5.28) in a group of NDIs, mean score baseline was 35.97 (SD =4.34) and follow-up was 37.68 (SD=4.43) in a group of PDIs and mean score baseline was 41.00 (SD=3.06) and follow-up was 33.00 (SD=1.73) in a group of ADIs, respectively. The pair t – test indicated no significant difference between mean score in NDIs group (t = 1.876, p = 0.064). The significant difference between mean score was detected in PDIs group (t = -2.079, p = 0.045) and ADIs group (t = 5.237, p = 0.035), shown in Table 4.10

Table 4.10 Mean score of SF -12 in groups of NDIs and DIs

DIs Group	SF-12 Base line scores		SF-12 Follow – up scores		t	df	p - value
	Mean	SD	Mean	SD			
NDIs (97 cases)	37.33	4.12	36.07	5.28	1.876	96	0.064
PDIs (38 cases)	35.97	4.34	37.68	4.43	-2.079	37	0.045
ADIs (3 cases)	41.00	5.29	33.00	3.00	5.237	2	0.035

In aspect of psychosocial, psychosocial form (Appendix IV) was used to evaluate. The questionnaire was composed of 42 questions, classified into 14 domains, scores of each domain varied from 0 to 20 and negatively correlated. Mean scores and SD were shown in Table 4.11. Due to mean scores were not in normal distribution, nonparametric statistic, Mann – Whitney test was performed in this result. Mean rank and Wilcoxon signed ranks test of psychosocial in groups of NDIs, PDIs and ADIs were shown Table 4.12 and Table 4.13, respectively.

In a group of NDIs, the follow – up scores in 10 domains was less than baseline except domain of adverse of leisure, problems with taking medication, distrust of the medical profession and depression of emotional reaction. After mean scores comparison, 3 domains (attitude towards accepting the seizure, lack of confidence about the future and lack of confidence about traveling) that follow – up mean scores were less than baseline significantly.

In a group of PDIs, the follow – up scores in 13 domains was less than baseline except domain adverse reaction of social life. After mean scores comparison, 5 domains (fear of stigma in employment, lack of confidence about the future, change of outlook on life/self, difficulty communicating with family and problems with taking medication) that follow – up mean scores were less than baseline significantly.

In a group of ADIs, the follow – up scores in 12 domains was less than baseline except domains of adverse reaction on social life and lethargy/lack of energy. After mean scores comparison, no significant difference between baseline and follow – up mean scores were found.

Table 4.11 Mean score of psychosocial in epilepsy patients classified by drug interaction

Domain[a]	Total (n = 138 cases)				NDI (n = 97 cases)				PDI (n = 38cases)				ADI (n = 3 cases)			
	Baseline		Follow – up		Baseline		Follow – up		Baseline		Follow – up		Baseline		Follow – up	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	11.493	9.996	9.489	9.347	11.432	10.310	9.377	9.294	11.077	9.426	9.660	9.811	16.818	7.417	10.625	8.253
2	14.264	11.201	13.460	12.236	13.921	11.245	13.808	11.622	14.833	11.277	12.462	14.240	17.342	11.690	14.247	8.038
3	9.263	10.533	7.118	8.500	9.332	10.233	8.152	9.212	8.677	11.123	4.239	5.709	13.005	14.412	8.664	7.250
4	9.350	9.821	5.747	7.842	10.431	10.071	6.494	8.360	6.713	8.489	3.971	6.377	7.540	12.922	4.053	4.804
5	9.560	9.948	7.227	6.887	8.798	9.245	6.901	6.664	11.541	11.531	7.564	7.387	9.685	10.997	12.009	7.411
6	10.186	9.830	9.977	9.920	10.056	10.047	9.405	9.609	10.170	9.494	11.341	10.774	13.507	9.256	11.241	10.512
7	10.576	10.626	11.613	10.258	9.690	10.331	11.890	10.919	12.617	11.536	10.828	8.763	13.201	7.593	12.343	5.861
8	11.173	10.143	9.201	8.444	10.836	10.068	9.442	8.554	12.184	10.385	8.696	8.223	9.922	11.899	8.032	9.815
9	5.369	8.105	3.965	6.415	4.660	7.269	4.298	6.833	6.837	9.778	3.141	5.374	8.996	10.095	3.525	5.143
10	7.009	8.750	6.293	9.069	6.256	7.735	6.519	9.058	8.498	10.706	5.100	8.822	11.312	11.414	11.845	11.671
11	4.612	7.338	3.788	6.618	4.185	6.641	4.277	7.137	4.968	8.427	2.426	4.616	11.686	11.026	4.555	9.109
12	11.175	10.671	10.560	10.062	10.392	9.859	10.849	10.442	13.094	12.484	9.906	9.327	12.413	12.350	9.612	9.014
13	11.150	10.268	8.190	8.764	10.805	10.550	8.380	9.321	11.419	9.721	8.149	7.301	18.996	5.074	3.943	7.886
14	12.081	9.278	10.684	9.487	11.455	8.839	10.332	9.350	13.800	10.435	11.819	9.912	11.366	8.610	8.740	10.389

(a ; 1:Attitude towards accepting the seizures, 2:Fear of having seizures, 3:Fear of stigma in employment, 4:Lack of confidence about the future, 5:Lack of confidence about traveling, 6:Adverse reaction on social life, 7:Adverse reaction on leisure 8:Change of outlook on life/self, 9:Difficulty communicating with family, 10:Problems with taking medication, 11:Distrust of the medical profession, 12:Depression or emotional reactions, 13:Feeling of increased social isolation, 14:Lethargy/lack of energy)

Table 4.12 Mean rank and sum of ranks between follow – up and baseline of psychosocial aspects

[F – B] Domain	NDI				PDI				ADI			
	Mean rank		Sum of ranks		Mean rank		Sum of ranks		Mean rank		Sum of ranks	
	Negative rank	Positive rank	Negative rank	Positive rank	Negative rank	Positive rank	Negative rank	Positive rank	Negative rank	Positive rank	Negative rank	Positive rank
[F – B]^{1}	41.72	37.15	2044.50	1114.50	18.79	15.87	357.00	238.00	2.50	1.00	5.00	1.00
n	49	30	49	30	19	15	19	15	2	1	2	1
[F – B]^{2}	40.81	46.89	1959.00	1782.00	16.77	17.45	369.00	192.00	3.00	1.50	3.00	3.00
n	48	38	48	38	22	11	22	11	1	2	1	2
[F – B]^{3}	39.38	34.12	1575.00	1126.00	15.58	7.86	296.00	55.00	2.00	2.00	4.00	2.00
n	40	33	40	33	19	7	19	7	2	1	2	1
[F – B]^{4}	38.37	28.33	1918.50	566.50	12.88	11.57	219.00	81.00	2.00	1.00	2.00	1.00
n	50	20	50	20	17	7	17	7	1	1	1	1
[F – B]^{5}	40.38	34.43	1817.00	1033.00	18.12	15.04	380.50	180.50	2.00	2.00	2.00	4.00
n	45	30	45	30	21	12	21	12	1	2	1	2
[F – B]^{6}	39.72	36.22	1510.00	1340.00	16.47	16.53	247.00	281.00	1.00	2.00	1.00	2.00
n	38	37	38	37	15	17	15	17	1	1	1	1
[F – B]^{7}	38.09	42.63	1104.50	2216.50	18.57	13.59	278.50	217.50	2.00	1.00	2.00	1.00
n	29	52	29	52	15	16	15	16	1	1	1	1

Table 4.12 (continued) Mean rank and sum of ranks between follow – up and baseline of psychosocial aspects

[F – B] Domain	NDI				PDI				ADI			
	Mean rank		Sum of ranks		Mean rank		Sum of ranks		Mean rank		Sum of ranks	
	Negative rank	Positive rank	Negative rank	Positive rank	Negative rank	Positive rank	Negative rank	Positive rank	Negative rank	Positive rank	Negative rank	Positive rank
[F – B]^{8}	41.73	41.19	1961.50	1441.50	16.88	14.15	354.50	141.50	1.50	0.00	3.00	0.00
n	47	35	47	35	21	10	21	10	2	0	2	0
[F – B]^{9}	26.87	28.29	806.00	679.00	13.41	8.00	228.00	48.00	2.50	1.00	5.00	1.00
n	30	24	30	24	17	6	17	6	2	1	2	1
[F – B]^{10}	32.29	34.78	1098.00	1113.00	13.44	11.86	242.00	83.00	2.00	1.00	2.00	1.00
n	34	32	34	32	18	7	18	7	1	1	1	1
[F – B]^{11}	27.38	29.70	794.00	802.00	10.69	8.50	139.00	51.00	2.00	0.00	6.00	0.00
n	29	27	29	27	13	6	13	6	3	0	3	0
[F – B]^{12}	33.42	45.70	1403.50	1599.50	17.94	11.83	323.00	142.00	2.00	1.00	2.00	2.00
n	42	35	42	35	18	12	18	12	1	1	1	1
[F – B]^{13}	40.44	33.42	1739.00	1036.00	19.08	11.73	343.50	152.50	2.00	1.00	2.00	1.00
n	43	31	43	31	18	13	18	13	1	1	1	1
[F – B]^{14}	46.02	41.39	2255.00	1573.00	17.61	16.18	334.50	226.50	1.00	2.00	1.00	2.00
n	49	38	49	38	19	14	19	14	1	1	1	1

Table 4.13 Wilcoxon signed ranks test of psychosocial different scores

[F – B] Domain	NDI (n = 97 cases)		PDI (n = 38cases)		ADI (n = 3 cases)	
	Z [d]	P value	Z [d]	P value	Z [d]	P value
[F – B][1]	-2.271	0.023	-1.018 [a]	0.309	-1.069 [a]	0.285
[F – B][2]	-3.81 [a]	0.703	-1.582 [a]	0.114	0.000 [c]	1.000
[F – B][3]	-1.234 [a]	0.217	-3.062 [a]	0.002	-0.535 [a]	0.593
[F – B][4]	-3.957 [a]	0.000	-1.974 [a]	0.048	-0.447 [a]	0.655
[F – B][5]	-2.071 [a]	0.038	-1.787 [a]	0.074	-0.535 [b]	0.593
[F – B][6]	-0.449 [a]	0.653	-0.318 [b]	0.751	-0.447 [b]	0.655
[F – B][7]	-2.619 [b]	0.009	-0.598 [a]	0.550	-0.447 [a]	0.655
[F – B][8]	-1.202 [a]	0.229	-2.088 [a]	0.037	-1.414 [a]	0.157
[F – B][9]	-0.547 [a]	0.584	-2.739 [a]	0.006	-1.069 [a]	0.285
[F – B][10]	-0.048 [b]	0.962	-2.140 [a]	0.032	-0.447 [a]	0.655
[F – B][11]	-0.033 [b]	0.974	-1.772 [a]	0.076	-1.633 [a]	0.102
[F – B][12]	-0.498 [b]	0.619	-1.862 [a]	0.063	-0.447 [a]	0.655
[F – B][13]	-1.895 [a]	0.058	-1.875 [a]	0.061	-0.447 [a]	0.655
[F – B][14]	-1.444 [a]	0.149	-0.965 [a]	0.334	-0.447 [b]	0.655

[F – B] = (Follow - up score) – (Baseline score) , a = Based on positive ranks, b = Based on negative ranks, c = The sum of negative ranks equals the sum of positive ranks,d = Wilcoxon signed ranks test

Chapter V

Discussion

This study was performed to prospectively assess the magnitude of DIs during ten – month period and comparing the QOL before and after DIMs by pharmacist. After DIMs, of 312 cases enrolled in the study, prevalence of DIs was 27.88% (87 cases), which can be devided into 2 categories; 26.28% (82 cases) of PDIs and 1.60% (5 cases) of ADIs.

The result was shown a positively significant correlation between numbers of medications and DIs presentations. In epilepsy patients, administered AEDs and/or other drugs from 2 to 7 items, prevalence of DIs was increased from 8.00% to 80% (Table 4.3). This result was in line with the previous finding that the risk of DIs increased with number of medication.[85]

Chronic disease, such as Auto Immune Deficiency Diseases (AIDs), where patients offer taking 10 or more drugs, develops the chances of DIs. Controversy, the treatment of epilepsy with single medication is a satisfactory therapeutic strategy in about 70% of patients. In most of the remaining patients long term AEDs polytherapy is used.[86]

Epilepsy patients in this study (312 cases) were prescribed medications ranging from 2 to 7 items, both the medications in average in group of PDIs (4.74 ± 1.36) and ADIs (4.00 ± 0.71) were more than NDIs (3.17 ± 1.06) (Table 4.4). This result confirmed with the previous study that the number of potential DIs increased with the number of prescribed drugs.[4] Furthermore, it was found that number of medication in average among three groups were significantly difference ($p < 0.001$). However,

number of medication in average in case presented with PDIs and ADIs were not significantly difference, may be cause of limitation of sample in cases presented with ADIs, only 5 cases in this study.

Three hundreds and twelve prescriptions from 312 cases were enrolled to identify drug groups which favorable prescribed in epilepsy clinic, the most favorable AED was PB (203 cases, 65.06%), PHT (196 cases, 62.82%) and CBZ (130 cases, 41.67%), respectively. All of them were first generation AEDs that high tendency to present D - DIs more than second generation or newer AEDs, owing to the characteristic of CYP P450 enzyme inducers. This study found that antianemic drug, folic acid (199 cases, 63.78%) was mostly prescribed with AEDs. Replacement of folic acid in folate deficient patients taking inducing AEDs may increase the metabolism with a resultant decrease in serum concentration of PHT. Decreases in serum PHT were noted in 3 of 4 normal subjects when folic acid 10 mg per day was added to PHT 300 mg per day.[81] Also, folic acid given to a patient on PHT therapy was followed by a decrease in serum PHT concentrations to subtherapeutic levels and an increase in seizure frequency. In this clinic, small doses of folic acid (5 mg per day) corrected inducing AEDs induced folate deficiency, these combinations were concluded as NDIs presentations.

In this study, significant DIs consideration between AEDs polytherapy was focused on LTG coadministered with VPA. In our study, this combination was not found in epilepsy clinic, due to generalized tonic clonic (147 cases, 47.1%) was prominent type which be controlled by first line drug, PHT and newer AEDs, TPM and GBP were mostly adjunctive prescribed drugs especially for refractory seizure.

In cases presented with PDIs, classified into 101 events (32 DDIs) of pharmacokinetic from total DDIs (90 DDIs), majority of the mechanism was metabolic processes (29 DDIs, 90.63%) (Table 4.6). The severity of DIs in 20 DDIs (59 events, 58.42%) was moderate and 12 DDIs (43 events, 42.57%) was minor with no severe case. Pharmacodynamic PDIs were classified into 182 events from 58 DDIs, mostly mechanism was additive interaction and combined toxicity (30 DDIs, 51.72%), following to 33 events (17 DDIs, 29.31%) of antagonistic mechanism and 51 events (10 DDIs, 17.24%) of both mechanisms combination (Table 4.7). Although Pharmacodynamic were detected more than pharmacokinetic PDIs but the severity was minor of no significantly important in this study.

Physician and pharmacist should aware of this pharmacodynamic DIs when additive interaction was started especially in elderly and renal or hepatic impaired patients. Antagonistic mechanism should also be avoid in intractable epilepsy, if impossibly, slowly dosage escalation and closely monitor be performed participately.

BZPs are a large class of compounds, some of which are used as AEDs. Undoubtedly, BZDs was found to be the most prescribed drugs with AEDs in this study. In particular, DZP, LZP and midazolam are used for acute treatment of status epilepticus and serial seizure, while CZP, nitrazepam, clobazam and clorazepate are used for adjunctive chronic antiepileptic therapy. BZDs are mainly eliminated by metabolism, especially by CYP P450 or uridine diphosphate glucuronosyltransferase reactions, and are highly bound to plasma proteins. These characteristics make these drugs a likely target for pharmacokinetic interactions. On the other hand, they exhibit a low capacity to modify the disposition of other AEDs. Indeed, inducer AEDs have been shown to increase the clearance of clobazam, DZP, CZP, and clorazepate – derived *N* – desmethyldiazepam, lowering their plasma concentrations. For clobazam, this

interaction leads to an accumulation of the pharmacologically active *N* – desmethyl metabolite.

Moreover, VPA may displace BZDs plasma protein binding and may inhibit their metabolism.[49] Some possible evidences of BZDs toxicity induced by VPA were reported, but generally interaction is of limited clinical importance. In any case patients on long term BZDs starting VPA cotherapy should be carefully monitored and BZDs dosages should be reduced if signs of toxicity appear. In this study, DZP (26 cases, 8.33%) was mostly combined with AEDs and other drugs such as antipsychotics, antidepressants and beta – blockers. For patients with stress and insomnia precipitated seizure, low dose of alprazolam (6 cases, 1.92%) and LZP (5 cases, 1.60%) were introduced in this therapy. For adjunctive cataminial and chronic epilepsy therapy, clobazam and clorazepate were administered in 6 cases (1.92%) and 3 cases (0.96%), respectively. For all these cases, long term combination of AED(s) and BZD(s), there is no report in decreasing BZDs efficacy. However, physicians attempted to diminish the dosage during therapy. Only one case, 42 – year – old man with generalized seizure, receiving PHT 300 mg, PB 30 mg and DZP 5 mg per day with drinking habit, patient experienced insomnia so DZP was finally steped up from 5 mg to 10 mg. This result could not definitely concluded as ADIs according to:

1) Long term combination of 5 mg of DZP and 300 mg of PHT for 5 years

- Normally, the time required to induction depends on both the time need to reach steady – state of the inducing agent and the synthesis rate of new enzymes. Testing reports have probed for CYP 3A induction, 6β – hydroxylation of cortisol. Multiple dose PHT administration caused a rapid increase in the urinary 6β – hydroxycortisol/cortisol ratio, with an apparent induction plateau achieved after approximately 4 days.[87] Result of induction in this case should be occurred

approximately in 7 days. Moreover, DZP has an active metabolite (desmethyldiazepam), induction can result in an elevation of metabolite concentrations resulting in an increase of drug's therapeutic effect and toxicity. In this case, increasing of dosage likely caused by drug resistant.

2) Drinking habit

- Alcohol acts as inducer of CYP 3A4. Both PHT and DZP metabolisms were induced resulting in a decrease in their efficacy.

3) The absence of plasma concentration of DZP

- No plasma concentration of DZP was recorded, it did not show an increase of DZP clearance.

This patient was categoried as PDI instead of ADI since there was no sign of PHT toxicity such as ataxia, nystagmus and confusion eventhough DZP seems to inhibit PHT metabolism resulting in an increasing of its plasma concentrations in some patients. The interaction mechanism may result from the competition of CYP 2C19 catabolic pathway. However, the problem of insomnia disappeared when drinking was prohibited, and PHT level went to therapeutic index. We can conclude that the critical interaction in this case was alcohol and drugs (PHT and DZP) due to the fact that alcohol acts as an inducer of CYP P450, especially CYP 3A4. Future study of DIs, the absence of drinking habit was assigned in criteria, prevention of alcohol and drugs interaction.

TCAs were favorable antidepressants which prescribed in epilepsy patients. In this study, amitriptyline was the most prescribed agent (20 cases, 6.41%) following by to nortriptyline (1 case, 0.32%) and imipramine (1 case, 0.32%) (Table 4.5). The dosage varied from 10 mg to 25 mg. The anticonvulsants PB, PHT, and CBZ are potent liver enzyme inducers which can result in decreasing plasma levels and therefore decreasing the efficacy of antidepressants metabolized by the same isoenzymes. Clinically

significant interactions are reported with TCAs.[88] Most of the older antidepressants, especially the TCAs, mianserine, and trazodone, produce sedative side effects. This may be particularly troublesome to patients taking AEDs known to cause sedation, such as PB and BZPs. Besides, there is a report suggests that sedative antidepressants are more epileptogenic.[89] Sedative antidepressants may be given to patients with co – existent anxiety or agitation but they may result in daytime drowsiness and impaired psychomotor function. However, in this study, we did not find an increase incidence of seizure related to antidepressants and some patients even demonstrated improved control, due to low dosage of antidepressants, 10 mg of amitriptyline or 25 mg of imipramine per day was prescribed to epilepsy patients.

The incidence of seizures occurring with therapeutic dose of antidepressants varies from 0.1 to 4%.[89] This needs to be compared to the annual incidence of first seizures in the general population, estimated at 0.073 – 0.086%.[89] Preskorn and Fast also noted that they could not find any reports of TCA – induced seizures at therapeutic plasma concentration and concluded that patients who experienced convulsions at the therapeutic dose of antidepressants were likely to be slow metabolizers of the drugs.[90] Seizure is more likely to occur during the first week of antidepressant treatment or after an increase in dose, especially after rapid dose escalation.

Although omeprazole was a potent enzyme inhibitor of CYP 2C and interaction potency was dose dependent, but no significant interaction was detected. Omeprazole 20 mg for peptic ulcer together with PHT 300 mg and VPA 500 mg per day for complex partial seizure were prescribed. One month latter, horizontal nystagmus was observed and total phenytoin level was 16 μg/ml. After dechallenge of omeprazole, total PHT level was unlikely change (15 μg/ml) and horizontal nystagmus was disappeared. Again, in this case can be classified as only PDI. In the future study,

baseline total phenytoin concentration together with serum albumin should be monitored in order to compare the level before and after drug interaction was detected. This interaction was not clinical significant, since low dose of omeprazole (20 mg per day) was taken. Similarly, preliminary evidence suggests that smaller doses of omeprazole (20 mg daily) have minimal effects on PHT plasma concentration.[81]

As new classes of antimicrobial drugs become available, pharmacokinetic DIs with antimicrobials become more common. Macrolides, fluoroquinolones, rifamycins, azoles and other agents can interact adversely with common used drugs, usually by altering their hepatic metabolism.[91] In this study fluoroquinolones, ciprofloxacin was prescribed with CBZ. However, standing seizure frequency and no sign of CBZ toxicity were detected. Since ciprofloxacin appears to be selective inhibitor of CYP 1A2, however, CBZ is a substrate and be metabolized mainly by CYP 3A4, therefore, no signs and symptoms of CBZ toxicity including nausea, vomiting, drowsiness, confusion, nystagmus, ataxia, and seizure were observed.

The most common pharmacokinetic interactions cause by an inhibitory effect of the SSRIs on the hepatic CYP P450 metabolic system. It has become apparent that SSRIs are potent inhibitors of CYP isoenzymes. This inhibition is concentration – dependent. Factors that determine blood concentrations, and thus the degree of CYP inhibition, include[92]:

(1) dosage – inhibition is greater at higher doses

(2) age – some SSRIs (e.g. citalopram and paroxetine) demonstrate an age – related increase in plasma concentration

(3) clearance – all of the SSRIs show reduced clearance in the presence of significant hepatic or renal disease

(4) metabolites – in general, the N – demethylated metabolites of the SSRIs have a

similar potency to the parent compounds in inhibiting CYP function. Exceptions to this latter factors are paroxetine (metabolites vary greatly in CYP inhibition potency, with M2 being a particularly strong inhibitor of CYP 2D6) and fluoxetine (norfluoxetine inhibits CYP 3A4, in contrast to fluoxetine, which has a minimal effect on this enzyme). The CYP inhibition potency is unrelated to the activity of these metabolites in inhibiting serotonin reuptake.

PHT is hydroxylated primarily by CYP 2C9/10 and secondarily by CYP 2C19. Shader et alreported a mean elevation of 160% in PHT levels after the addition of fluoxetine.[93] Levy using S − warfarin and tolbutamide as probes for CYP 2C9, attributed the effect of fluoxetine on PHT metabolism to an inhibition of CYP 2C19.[94] There have also been reports of neurotoxicity with this combination.[95] Sertraline dose not appear to affect the kinetics of PHT.[96] Levy determined that CYP 3A3/4 is the major enzyme catalysing formation of the epoxide metabolite of CBZ.[94] Numerous reports of the effect of SSRIs on CBZ metabolism have been published. Fluoxetine flovoxamine and sertraline have all been reported to increase CBZ concentration and produce symptoms of neurotoxicity[96-98], though Rapeport et al were unable to demonstrate any effect of sertraline on the pharmacokinetics or pharmacodynamics of this anticonvulsant.[99] Dursan et al reported a patient who developed features consistent with the serotonin syndrome while receiving the combination of fluoxetine and CBZ. [100] Spina et al , however, reported no significant interactions associated with fluoxetine or fluvoxamine in a controlled study of patients with epilepsy who were prescribed CBZ.[101]

Similarly, in our study, no sign or symptom of PB toxicity was observed in a case administered PB and enzyme inhibitor; fluoxetine 10 mg per day. From previously mentioned, power of inhibition potentially increase at higher dosage level of fluoxetine

(more than 20 mg).[101] In this case, this epilepsy patient administered only 10 mg of fluoxetine dosage, predicted with PDI occurred.

Patient presented with generalized seizure and hypothyroidism, receiving of PB 60 mg and thyroxine 100 μg per day, seizure free for more than 2 years and T_3 (triiodothyronine) went up from 1.04 ng/dl at baseline to 1.12 ng/dl. Free T_4 (Sodium-1-thyroxine) went up from 1.11 ng/dl at baseline to 2.14 ng/dl, and TSH (Thyroid Stimulating Hormone) elevated from 0.03 ng/dl at baseline to 0.36. Although PB increases nondeiodinative T_4 clearance, no significant interaction was observed in this case. This may be dued to low dosage of PB and TDM was performed after 1 year of combination. Theoretically, the metabolic breakdown of endogenous and exogenous thyroxine is accelerated. Patients whose hypothyroidism has previously been controlled may need an increase in thyroxine dosage if PB administered.[81]

In additive interaction and combined toxicity, possible results were increasing of central nervous system (CNS) depression such as drowsiness, confusion and sedation. Interacting drugs were conventional AEDs (PHT, PB, CBZ) and BZPs, TCAs, antipsychotic, antihistamine and muscle relaxant drugs. In this study, addition of CNS depression did not present distinctly due to long term combination made this patient accustomed to addition of CNS depression. Visual analogue scale (Appendix VI) was applied to detect DIs. The difference scores did not present obviously (decreased less than 50 %) in cases discharge of interacting drugs. A subject of 25 – years – old man with complex partial seizure received CBZ 800 mg, TPM 100 mg and CZP 3 mg per day. Seizure frequency was at least 1 time per day or more than 7 times per week. This patient received ciprofloxacin 750 mg, calcium carbonate 1,500 mg and tramadol 150 mg for the treatment of broken leg bone from accident together with AEDs. The difference score was unchange (score = 4, very drowsy) although tramadol was

discharged. In this case the score was consistent which maybe caused by addition of TPM from 100 mg to 125 mg per day and high dose of CZP. Further study in visual analogue scale should be applied to measure severity of CNS depression when patients have static condition, especially at initiation stage of using combination drugs.

This study found that ADIs (5 cases, 1.60%) occurred during metabolic stage, pharmacokinetic interactions. Four cases of ADIs interacted with contraceptives and hormones. A wide variety of anticonvulsants can cause contraceptive failure when given to women taking oral contraceptives (OCs). Reports of committee on Safety of Medicines (CSM) in the UK between 1968 and 1984, anticonvulsants that have been implicated in case of contraceptive failure in women taking OCs were ordered following: PHT (25 cases) > PB (20 cases) > primidone (7 cases) > CBZ(6 cases) > VPA (1 case).[102] Owing to the limitation of subjects and period of collection, this study found that CBZ (2 cases) > PB (1 case) and PHT (1 case) interacted with OCs. Breakthrough bleeding was a reasonable clinical sign of relative estrogen deficiency, although the fall in blood level of ethinyloestradiol did not perform. However, in the past history of those patients, other OCs were applied but breakthrough bleeding still occurred during cotreatment with this inducing AEDs. Although OCs and AEDs were taken for conception in 3 epilepsy women during 1 - 3 years, breakthrough bleeding and spotting occurred during using the combination, but unwilling pregnancy was not informed. Breakthrough bleeding and spotting were disappeared when dechallenge of OCs, but rechallenge was not performed in this cases since the patients used other methods for conception.

OCs are not associated with exacerbation of epilepsy.[102] However, it can not be absolutely concluded in this study due to the fact that all subjects using OCs had experience of seizure at least 1 time and less than 12 times per year. Further prospective

data in these cases should be collected. The effectiveness of hormonal contraceptives, however, can be reduced by enzyme – inducing AEDs (CBZ, PHT, PB, felbamate, TPM). Hormonal contraceptives are available in three formulations which are oral (estrogen–progesterone combinations or progesterone only), subcutaneous (Levonorgestrel) or intrauterine implants (Progestacert® or Mirena®), and injectable (medroxyprogesterone acetate suspension). All three forms can be adversely affected by enzyme – inducing AEDs. Physician and pharmacist should advise epilepsy patients to choose other methods for conception such as condom, intrauterine devices, spermicide to avoid contraceptive failure.

AEDs may lower concentrations of estrogens by 40 – 50%. Therefore, the lower – or mini – dose of OCs should be avoid. Midcycle spotting or bleeding indicates ovulation is not suppressed especially when OCs contain less than 50μg of estrogen. Contraceptive failure may not always be predictable, even when midcycle spotting does not occur. Failure of basal body temperature to rise at midcycle can be used to document ovulatory suppression. Alternatively, nonenzyme – inducing AEDs such as VPA, LTG and GBP may need to be considered. Also, a coordinated approach by obstetricians, gynecologists, neurologists and pharmacists is important in promoting optimal treatment and adequate patient education.

In this study, Anamai® (norethisterone 1 mg and mestranol 0.05 mg) was used in 2 subjects and Anna® (levonorgestrel 150 μg and ethinylestradiol 30 μg) was used in 1 subject with AEDs, showing a lack of contraceptive efficacy and also irrigular or breakthrough menstrual bleeding. Oral contraceptive doses can be increased to compensate for the effect of AEDs. However, increase of ADR and toxicity of high dose OCs prohibit most physicians from increasing the dosage. Especially, women

older than 35 years of age or those who smoke must consider the risk of thromboembolic complications associated with higher doses of contraceptives.[102]

In case taken the combination of PHT 200 mg for complex partial seizure and estrogen 0.625 mg per day for control hot flush due to menopause, failure of hormone supplement was observed after 2 months using the combination. This dues to PHT induces metabolism of estrogen through CYP 3A4. To eliminate this DIs, VPA was gradually added meanwhile reducing the dose of PHT. VPA was an alternative AED, since did not interact with hormones and OCs.[102] After completely dechallenge of PHT, symptom of hot flush was disappeared.

Anticoagulant drug, warfarin, was prescribed in 29 – year – old women presented with post partum seizure caused by deep vein thrombosis. This subject was given 2 medications which are PHT 300 mg and warfarin 6.5 mg per day. The baseline international ratio (INR) was 1.28. After 1 month, INR decreased to 1.18 resulting in warfarin dosage increased to 7.5 mg per day. Physician planed to reach target INR by decreasing PHT gradually 50 mg per month. At 250 mg per day of PHT dosage, INR was reached to 1.5. Finally, when PHT was discharged and warfarin dosage was decreased to 5 mg per day, INR went up to 1.97. Warfarin is a substrate of CYP 2D6 which induced by PHT, anticoagulant effect of warfarin was deteriorated. Since this case presented with post partum seizure only 1 time and low risk of recurrence, decline dosage of inducing AED was applied. However, patients with high risk of seizure, PHT should be replaced with alternative AED such as VPA or second generation AEDs (TPM, GBP and OXC). In other words, increasing warfarin dosage was reasonable but ADR monitoring was also necessary.

After QOL assessment, 138 patients were classified into 3 groups, NDIs (97 cases), PDIs (38 cases) and ADIs (3 cases). In aspect of adverse events of AEDs, the questionnaire (Appendix II) was used for evaluation. The range of scores varied from 0 to 38 and negatively correlated. Baseline mean scores of adverse events in PDIs group (10.66) were higher than in NDIs group (10.40). Since PDIs group received several medications, has higher tendency to increasing incidence of adverse events. Especially, first – generation AEDs were favorable prescribed in this clinic. The pair t – test indicated no significant difference between baseline and follow – up mean score in both groups. However, mean scores in both groups had lower tendency, it meaned that occurrences of adverse events likely decreased. In ADIs group, the higher scores were observed, maybe due to dosage and duration adjustment, usage of alternative drugs were applied to avoid DIs. However, the increased scores were lower than other groups and no significant difference from baseline.

In aspect of general health, SF - 12 form (Appendix III) was used to evaluate. The range of scores varied from 12 to 51 and positively correlated. Baseline mean scores of general health in a group of ADIs were higher than NDIs and PDIs, but follow – up mean scores of general health in a group of ADIs were lower than others (Table 4.10). Higher scores in a group of PDIs were observed significantly. Since period of time (no longer than 3 months) was limited, so it was difficult to detect obvious changes of scores. Moreover, seizure free presented 32.99% (32 cases) in a group of NDIs, 26.83% (11 cases) in PDIs and no found in ADIs. The better control of seizure is a key to improving the QOL of people with epilepsy.[103]

In a group of NDIs, follow – up scores of general health were lower than baseline, but no significant difference. Since more than 70% in NDIs group suffered

from seizure at least 1 time per year. Consequently, decreasing of scores may caused by disease related factors.

The data of psychosocial aspect was not normal distribution, nonparametric performed in this part. In aspect of psychosocial, psychosocial form (Appendix IV) was used for evaluation. The questionnaire was composed of 42 questions, classified into 14 domains, score of each domain varied from 0 to 20 and negatively correlated. All of 3 groups, more than half of all domains had lower potency of follow – up scores than baseline except 4 domains of NDIs, 2 domains of ADIs, and only 1 domain in PDIs groups, respectively (Table 4.11). In a group of ADIs, the lower potency of scores in these domains increased were observed but no significant difference. It was not an apparent change of psychosocial, because there were only 3 subjects in a group of ADIs and short period of assessments (2.36 months, SD = 0.3138). After DIMs, it could not improved the domain which related to the problems of taking medication. In some cases, this adjustment may be confusion for patients to follow to the therapy regiment. In future study, follow – up scores was assessed after patients were familiar with new adjusted dosage or alternative medication.

In a group of PDIs, after DIMs, the scores of all domains improved distinctly. Exception of the domain of adverse reaction on leisure, the score did not improved but higher score was no significant difference.

All of above, although DIMs did not improved all domains of psychosocial, but in both groups of PDIs and ADIs had improved several domains more than NDIs group. In future study, more subjects especially in both groups of PDIs and ADIs should be collected for assessment, and DIMs should be performed in multicentre.

Epilepsy is characterized by uncertainty and its severity and prognosis are variable. Because of its clinical uncertainty and social meaning, the impact of epilepsy on a person's QOL can be significant.[13] Several studiesevaluated the results of a pharmaceutical care by using an assessment of Health Related Quality of Life (HRQOL), owing to an objective of pharmaceutical care is for pharmacist to improve patients' HRQOL by optimizing medication therapy.[104 – 111] In this research, DIM which is a part of pharmaceutical care was performed, several improvement was found in several domains of the survey. However, likewise some studies,the clinical pharmacist intervention had no significant impact on HRQOL.[107 – 109] Although SF – 36 questionnaire was used to measure HRQOL in some studies, however, in Thailand, SF – 12 questionnaire was approved to be workable in epileptic patients.[78,109,111] The advantages were having little length and uncomplicated questionnaire.

The ability, knowledge and experience of clinical pharmacist who monitored DIs also affected to DIs detection which mostly subjective data. Besides, outpatients which included into this study was a boundary. Loss of follow – up and noncompliance were noticed in outpatient clinic. They were difficulties monitoring side effects and adverse events that influenced from DIs appearance. Possibility, some patients experienced of some DIs might be tolerated or corrected by neurologists before DIM program.

Futhermore, in this study, the low presentation of DIs may partly due to the specialized clinic that neurologist interested in DIs awareness. Nevertheless, the challenge of interacted drugs was performed to conclude DIs appearance without a doubt.

Chapter VI

Conclusion

DIMs were prospectively monitored in outpatient department of epileptic clinic at Neurological Institute, during ten – month period. The objects were to determine prevelence of DIs of AEDs and AEDs – other drugs and to compare the QOL before and after DIMs by pharmacist. Three hundreds and twelve cases were enrolled in the study. Incidence of DIs was 27.88% (87 cases), which divided into 26.28% (82 cases) of PDIs and 1.60% (5 cases) of ADIs. Three hundreds and twelve prescriptions from 312 cases were enrolled to identify drug groups which favorable prescribed, the most favorable AED was PB (203 cases, 65.06%), PHT (196 cases, 62.82%) and CBZ (130 cases, 41.67%), respectively. Drugs which favorable prescribed with AEDs were folic acid (199 cases, 63.78%), BZPs (46 cases, 14.73%), vitamin & minerals (38 cases, 12.18%) and TCAs (22 cases, 7.05%), respectively. In this study, the combination of VPA and LTG was not found in this epilepsy clinic. In cases presented with PDIs, classified into 101 events of pharmacokinetic from total DDIs, majority of the mechanism was metabolic processes (90.63%). The severity of DIs in 20 DDIs (59 events, 58.42%) was moderate and 12 DDIs (43 events, 42.57%) was minor with no severe case. Pharmacodynamic PDIs were classified into 182 events of DDIs, mostly mechanism was additive interaction and combined toxicity (51.72%). This study found that ADIs (5 cases, 1.60%) occurred during metabolic stage, pharmacokinetic interactions. In this study, drugs which had ADIs were estrogens and warfarin.

Although, the interactions between OCs and AEDs which act as enzyme inducers were well – known in epileptic clinic, but this combinations also presented as ADIs in this study. Because of this occurrence, clinical pharmacist should educate

epileptic patients to avoid this interactions and participate with physicians in solving of DIs occurrence.

Out of 312 cases, 138 cases (44.23%) were enrolled for QOL assessment. QOL in aspect of adverse events of AEDs and general health showed an improvement of patients'QOL after DIMs by pharmacist in a group of PDI. In aspect of psychosocial, improvement of patients'QOL were observed in 13 domains of PDIs group and 12 domains of ADIs group. Although QOL was not improved significantly in all aspects of QOL, this study showed that most aspects of QOL were better than baseline after DIMs.

In ADIs, the domain related to the problems of taking medication was not improved after DIMs. This results maybe due to the fact that patients were not familiar with new adjusted dosage or alternative medication and be confused after the adjustment. In future study, the greater sample size and prolonged period of QOL assessment should be performed to confirm these results.

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APPENDICES

Appendix I

Drug interaction monitoring form record no. ☐☐☐☐

HN ☐☐ ☐☐☐☐☐

ก. ข้อมูลส่วนตัว

1. เพศ ☐ ชาย (0) ☐ หญิง (1) ☐

2. วันเกิด วัน ☐☐ เดือน ☐☐ ปี ☐☐☐☐

3. เชื้อชาติ (1) ไทย (2) จีน (3) อิสลาม(4) อื่นๆ..... ☐

4.สถานภาพสมรส (1) โสด (2) แต่งงาน (3) หย่าร้าง (4) อื่นๆ..... ☐

5.สถานะการศึกษา (0) ไม่ได้เรียน (1) ประถมศึกษา (2) มัธยมฯต้น (3) มัธยมฯปลาย ☐

(4)ปวช (5)ปวส(6)ประกาศนียบัตร(7) ปริญญาตรี (8)สูงกว่าปริญญาตรี

6.สถานะการงาน (0) ไม่ได้ทำงาน (1)มีงานประจำ (2)มีงานชั่วคราว ☐

7.กรณีมีงานระบุ (1) รับราชการ/รัฐวิสาหกิจ (2) ค้าขาย (3) รับจ้าง (4) อื่นๆ ..... ☐

8. รายได้ต่อเดือน (ต่อครอบครัวกรณีเป็นเด็ก) ..... บาท ☐☐☐☐☐☐

9. กรณีไม่ได้ทำงานแหล่งรายได้ (1) บิดา/มารดา (2) ญาติ ☐

(3) อื่นๆ .....

10. ดื่มเครื่องดื่มแอลกอฮอล์ (0) ไม่ดื่ม (1) ดื่มบ้าง ..... ครั้ง / เดือน

(2) ดื่มเป็นประจำ ระบุชนิด .....

ปริมาณแอลกอฮอล์ ..... กรัม / วัน ☐

กรณีที่ดื่มระบุ 10.1 ระยะเวลาที่เริ่มดื่มแอลกอฮอล์ (0) ระบุไม่ได้ (1) น้อยกว่า 1 เดือน

(2) น้อยกว่า 1 ปี (3) มากกว่า 1ปี ☐

11.สูบบุหรี่ (0)ไม่สูบ (1) สูบ น้อยกว่า 10 มวน/วัน ระบุ ..... มวน ☐

(2) สูบ มากกว่า 10 มวน/วัน ระบุ ..... มวน

12. ประวัติแพ้ยา (0) ไม่มี (1) ไม่แพ้แต่เกิดอาการข้างเคียงจากยา .....อาการ..... ☐

(2) แพ้ยาระบุ.....อาการ.....

13. น้ำหนัก ..... กิโลกรัม ส่วนสูง..... เมตร IBW..... ☐☐

14.ประวัติครอบครัว (0) ไม่มีโรคทางพันธุกรรม (1) มีโรคทางพันธุกรรม ระบุ..... ☐

ข.รายละเอียดโรคลมชัก

1. อายุที่เริ่มเป็นโรคลมชัก.....ปี ☐
2. ระยะเวลาที่เป็นโรคลมชัก.....ปี ☐☐
3. ชนิดของอาการชัก ☐
   - ❑ 3.1 focal seizure (0)
   - ❑ 3.2 focal turn 2nd GTC seizure (1)
   - ❑ 3.3 complex partial seizure (2)
   - ❑ 3.4 generalized seizure (3)
   - ❑ 3.5 specific syndrome (4)
   - ❑ 3.6 other or unclassified(5)

4. ชนิดของโรคลมชัก

- ❑ 4.1 idiopathic (1)
- ❑ 4.2 cryptogenic (2)
- ❑ 4.3 symptomatic (3)

5. ค่าเฉลี่ยความถี่ของการชักภายใน 1 ปีที่ผ่านมา

- ❑ 5.1 ไม่ชัก (0)
- ❑ 5.2 อย่างน้อย 1 ครั้งแต่น้อยกว่า 12 ครั้งปี (1)
- ❑ 5.3 อย่างน้อย 1 ครั้งต่อเดือน หรือมากกว่า 12 ครั้งปี (2)
- ❑ 5.4 อย่างน้อย 1 ครั้งต่อสัปดาห์ หรือมากกว่า 14 ครั้งต่อเดือน (3)
- ❑ 5.5 อย่างน้อย 1 ครั้งต่อวัน หรือมากกว่า 7 ครั้งต่อสัปดาห์ (4)

ค. ผลกระทบของโรคลมชัก

1. โรคลมชักทำให้ท่านมีความลำบากหรือมีผลกระทบต่อท่านในเรื่องใด (เลือกได้มากกว่า 1 ข้อ)

- ❑ ครอบครัว (1)
- ❑ อาชีพหรืองานที่ทำ (2)
- ❑ มิตรภาพต่างเพศ (3)
- ❑ การตั้งเป้าหมายในชีวิต 4)
- ❑ การเงิน (5)
- ❑ สัมพันธภาพกับผู้อื่น (7)
- ❑ การพึ่งพาตนเอง (8)
- ❑ อื่น ๆ (9) ระบุ .....

ง. ยาที่ใช้

1. ยาต้านอาการชัก

ชื่อยา	วิธีใช้	วันที่เริ่ม ใช้ยา							

2. ยาอื่น

ยาอื่นที่ใช้ชื่อยา	ข้อบ่งใช้	มีใบสั่ง	Drug interaction Definite	possible	วันที่เริ่มใช้				

จ. ค่าทางห้องปฏิบัติการที่เกี่ยวข้อง

ค่า lab									

ฉ.การวัดผลข้างเคียงของยารักษาโรคลมชัก

ครั้งที่ …… วันที่ …….. คะแนน……

ครั้งที่…….. วันที่ ……..คะแนน ……

ครั้งที่ …… วันที่ …….. คะแนน……

ครั้งที่…….. วันที่ ……..คะแนน ……

ครั้งที่…….. วันที่ ……..คะแนน ……

ตารางนัดผู้ป่วย เบอร์โทรศัพท์ …….. ช่วงเวลาที่สะดวกในการติดต่อ……

ที่อยู่……

ครั้งที่	วันที่	จำนวนรายการยาที่แนะนำการใช้ยา	การประเมินผ่าน ,ไม่ผ่าน	อาการและอาการแสดง	การแก้ไขหรือปรับเปลี่ยนยา

การให้คำแนะนำการใช้ยา

- ใช้เทคนิก Show and tell
- ประเมินผลโดยให้ผู้ป่วยอธิบายซ้ำ

note

Appendix II

ชื่อ ..... HN..... ประเมินครั้งที่ ..... วันที่ .....

ฉ.การวัดผลข้างเคียงของยารักษาโรคลมชัก

ในรอบ 4 สัปดาห์ที่ผ่านมาท่านมีปัญหาหรือมีอาการที่มีปัญหาต่อการทำงานหรือชีวิตประจำวันอย่างไร ถ้าท่านมีอาการเป็นประจำวงกลมข้อ 3 ถ้ามีอาการเป็นบางครั้งเลือกข้อ 2 เป็นต้น กรุณาตอบทุกข้อ

อาการ	เป็นประจำ	เป็นบางครั้ง	ไม่เป็นเลย
1.การทรงตัวไม่มั่นคง	2	1	0
2. เหนื่อยง่าย	2	1	0
3.ไม่อยู่นิ่ง	2	1	0
4.รู้สึกก้าวร้าว	2	1	0
5.กระสับกระส่าย	2	1	0
6.ปวดศีรษะ	2	1	0
7.ผมร่วง	2	1	0
8.มีปัญหาผิวหนังเช่น สิว , ผื่น	2	1	0
9. ตาพร่าหรือเห็นภาพซ้อน	2	1	0
10. ปั่นป่วนในท้อง	2	1	0
11.สมาธิไม่ดี	2	1	0
12.มีปัญหาเรื่องเหงือก	2	1	0
13.มือสั่น	2	1	0
14.น้ำหนักขึ้น	2	1	0
15.วิงเวียน	2	1	0
16.ง่วนนอน	2	1	0
17.ซึมเศร้า	2	1	0
18.มีปัญหาเรื่องความจำ	2	1	0
19.การนอนผิดปกติไปจากเดิม	2	1	0

Appendix III

General health questionnaire (SF – 12)

คำถามต่อไปนี้เกี่ยวกับสุขภาพของท่านโดยทั่วไปกรุณาตอบทุกข้อ

1.โดยทั่วไปท่านคิดว่าสุขภาพของท่าน

1.ดีมาก 2.ดีพอควร 3.ดี 4.ปานกลาง 5.ไม่ดีเลย

คำถามต่อไปนี้เป็นคำถามเกี่ยวกับชีวิตประจำวันที่ท่านอาจจะมีกิจกรรมต่างๆท่านคิดว่าสุขภาพของท่านมีผลจำกัดการดำเนินกิจกรรมต่างๆหรือไม่ ถ้ามี มีผลมากน้อยอย่างไร

	มีมาก	มีเล็กน้อย	ไม่มีเลย
2.การออกแรงระดับปานกลาง เช่น การยกโต๊ะ ใช้เครื่องดูดฝุ่น	1	2	3
3.เดินขึ้นบันไดหลายชั้น	1	2	3
4.กิจกรรมหนักๆ เช่น วิ่ง ยกของหนัก	1	2	3

ในระยะ 4 สัปดาห์ที่ผ่านมา ท่านมีปัญหาเกี่ยวกับงาน หรือกิจกรรมประจำวันเนื่องจากสุขภาพของท่านหรือไม่อย่างไร

	มีมาก	มีเล็กน้อย	ไม่มีเลย
5.สำเร็จได้น้อยกว่าที่ต้องการ	1	2	3
6.ลดเวลาที่ทำงานหรือกิจกรรมต่างๆ	1	2	3

ในระยะ 4 สัปดาห์ที่ผ่านมา ท่านมีปัญหาเกี่ยวกับการงาน หรือกิจวัตรประจำวันเนื่องจากอารมณ์ของท่าน เช่น ซึมเศร้า หรือกังวล มากน้อยอย่างไร

	มีมาก	มีเล็กน้อย	ไม่มีเลย
7.ไม่สามารถทำงาน หรือกิจวัตรต่างๆอย่างรอบคอบเช่นเคย	1	2	3

8.ในระหว่าง 4 สัปดาห์ที่ผ่านมา อาการปวด เช่น ปวดข้อ ปวดประจำเดือน รบกวนการงานตามปกติของท่านมากน้อยอย่างไร

1. ไม่เลย 2.เล็กน้อย 3.ปานกลาง 4.มากพอควร 5.มากที่สุด

คำถามต่อไปนี้เกี่ยวกับความรู้สึกและสิ่งต่าง ๆที่เกิดขึ้นกับท่านในระยะ 4 สัปดาห์ที่ผ่านมา

1.เป็นตลอดเวลา 2.เป็นเกือบตลอดเวลา 3.เป็นบ่อยๆ

4.เป็นครั้งคราว 5.เป็นเล็กน้อย 6.ไม่มีเลย

9.ท่านรู้สึกว่าสงบและเป็นสุข	1	2	3	4	5	6
10.ท่านรู้สึกว่าท่านมีพลังมาก	1	2	3	4	5	6
11.ท่านรู้สึกเหงาและเศร้าๆ	1	2	3	4	5	6

12.ในระหว่าง 4 สัปดาห์ที่ผ่านมา สุขภาพของท่านหรือปัญหาทางอารมณ์ของท่านรบกวนการเข้าสังคม เช่น การไปเยี่ยมเพื่อน หรือญาติ

1.ตลอดเวลา 2.เกือบตลอดเวลา 3.เป็นครั้งคราว

4.เป็นบ้างเล็กน้อย 5.ไม่มี

Appendix IV

Psychosocial questionnaire

คำถามต่อไปนี้มี 42 ข้อ ถามเกี่ยวกับความรู้สึกของท่านว่าอาการของโรคลมชักมีผลต่อท่านอย่างไร กรุณาตอบทุกข้อ โดยการกากะบาท x ในข้อที่ตรงกับความรู้สึกของท่านมากที่สุดดังนี้

0 คือ ไม่เคย หรือไม่มีผลเลย

1 คือ นานๆครั้ง หรือมีผลบ้าง

2 คือ เป็นบางครั้ง หรือมีผลบ้าง

3 คือ บ่อยครั้ง หรือมีผลมาก

4 คือ เกือบตลอดเวลา หรือมีผลมากที่สุด

1. ฉันลำบากใจที่จะยอมรับอาการของฉัน	0	1	2	3	4
2. ฉันไม่สะดวกที่จะอยู่เพียงลำพัง	0	1	2	3	4
3. มันยากที่จะบอกให้นายจ้างรู้ว่าฉันเป็นลมชัก	0	1	2	3	4
4. มันยากที่จะได้งานใหม่ เพราะอาการชักที่ฉันเป็นอยู่	0	1	2	3	4
5. ฉันไม่ต้องการที่จะโดยสารรถประจำทางเพราะว่าฉันอาจจะชักได้	0	1	2	3	4
6. ฉันต้องการที่จะออกไปข้างนอกน้อยลงเพราะว่าอาการของฉัน	0	1	2	3	4
7. ฉันรู้สึกว่ากิจกรรมในเวลาว่างของฉันเปลี่ยนไป เพราะว่าอาการของฉัน	0	1	2	3	4
8. ฉันรู้สึกว่าฉันมองชีวิตไปในทางลบเพราะว่าอาการชักของฉัน	0	1	2	3	4
9. ฉันรู้สึกลำบากที่จะพูดคุยกับครอบครัวเกี่ยวกับอาการชักของฉัน	0	1	2	3	4
10. ฉันรู้สึกว่า ฉันไม่ชอบการกินยา	0	1	2	3	4
11. ฉันรู้สึกว่าแพทย์ไม่ได้สนใจในสภาพอาการของฉัน	0	1	2	3	4
12. ฉันรู้สึกว่าชีวิตนี้ไม่มีค่าที่จะอยู่ เพราะอาการของฉัน	0	1	2	3	4
13. ฉันรู้สึกว่าไม่มีใครที่ฉันสนิทด้วยเนื่องจากอาการของฉัน	0	1	2	3	4
14. ฉันรู้สึกเพลียตลอดเวลาเพราะว่าอาการของฉัน	0	1	2	3	4
15. ฉันรู้สึกว่าอาการชักทำลายชีวิตของฉัน	0	1	2	3	4
16. ฉันเกลียดความคิดที่ว่าจะเกิดอาการชัก	0	1	2	3	4
17. ฉันรู้สึกว่าการเกิดอาการที่ทำงานอาจหมายถึงการถูกออกจากงาน	0	1	2	3	4
18. ฉันรู้สึกว่าฉันไม่สามารถแต่งงานได้เพราะว่าอาการของฉัน	0	1	2	3	4
19. ฉันรู้สึกว่าฉันไม่สามารถวางแผนสำหรับวันหยุดได้ เพราะว่าอาการของฉัน	0	1	2	3	4
20. ฉันรู้สึกว่าตัวฉันมีความสุขน้อยลงกว่าที่ควร เป็นเพราะอาการของฉัน	0	1	2	3	4

21. ฉันรู้สึกว่าฉันออกกำลังได้น้อยกว่าที่ควรเป็นเพราะอาการของฉัน	0	1	2	3	4
22. ฉันรู้สึกแปลกๆตั้งแต่เริ่มมีอาการ	0	1	2	3	4
23. ครอบครัวของฉันปฏิบัติต่อฉันเปลี่ยนไปเพราะอาการของฉัน	0	1	2	3	4
24. ฉันรู้สึกว่ายาที่ให้ฉันนั้นไม่มีประโยชน์	0	1	2	3	4
25. ฉันรู้สึกว่าหมอไม่รู้ว่ามีอะไรผิดปกติเกิดขึ้นกับฉัน	0	1	2	3	4
26. ฉันรู้สึกว่าสิ่งต่างๆทำให้ฉันแย่ลงตั้งแต่ฉันเริ่มมีอาการ	0	1	2	3	4
27. ฉันรู้สึกว่าเป็นภาระต่อผู้คนเพราะว่าอาการของฉัน	0	1	2	3	4
28. ฉันรู้สึกว่าทุกสิ่งต้องใช้ความพยายามขึ้นตั้งแต่อาการเริ่มปรากฏ	0	1	2	3	4
29. ฉันรู้สึกว่าฉันต่างไปจากคนอื่นๆเนื่องจากอาการของฉัน	0	1	2	3	4
30. ฉันรู้สึกไม่สะดวกที่จะไปไหน เพราะว่าอาจจะมีอาการเกิดขึ้นได้	0	1	2	3	4
31. ฉันรู้สึกอับอายเมื่อฉันมีอาการในที่ทำงานหรือที่สาธารณะ	0	1	2	3	4
32. ฉันรู้สึกว่ามันอาจจะเป็นความผิดที่ฉันมีลูก ทั้งนี้เพราะว่าฉันมีอาการชัก	0	1	2	3	4
33. ฉันต้องเตรียมการเดินทางเป็นพิเศษ เพราะอาการของฉัน	0	1	2	3	4
34. ฉันรู้สึกว่าฉันเข้าสังคมน้อยลงเพราะว่าอาการของฉัน	0	1	2	3	4
35. ฉันรู้สึกว่างานอดิเรกของฉันถูกจำกัดด้วยอาการของฉัน	0	1	2	3	4
36. ฉันรู้สึกมั่นใจกับอนาคตน้อยลง เพราะอาการของฉัน	0	1	2	3	4
37. ฉันรู้สึกว่าครอบครัวของฉัน ประณามฉันเรื่องอาการของฉัน	0	1	2	3	4
38. ฉันไม่ชอบที่ต้องกินยากันชัก	0	1	2	3	4
39. ฉันรู้สึกว่าการรักษาไม่น่าพอใจ	0	1	2	3	4
40. ฉันรู้สึกเครียด หรือเป็นกังวล เพราะว่าอาการของฉัน	0	1	2	3	4
41. ฉันพบว่ามันยากที่จะเข้ากับผู้คน	0	1	2	3	4
42. ในไม่ช้าฉันจะหมดกำลังเพราะว่าอาการของฉัน	0	1	2	3	4

Appendix V

Epilepsy diary

- ❑ Phase 1
- ❑ Phase 2

ชื่อผู้ป่วยนาย/นาง/นางสาว.....

ด.ช. / ด.ญ.

อายุ.....**ปี**

HN. ..... **เล่มที่** ...../.....

ที่อยู่.....

จังหวัด.....

เบอร์โทรศัพท์.....

ผู้บันทึก

- ❑ **ผู้ป่วย**
- ❑ **ผู้ดูแล**

มีปัญหาการใช้ยาติดต่อเบอร์ 0-224-600-59

ต่อ 2110 ภญ.เสริมสุขในเวลาราชการ

หรือ 0-998-240-66 นอกเวลาราชการ

(สมุดมีขนาด 10 x 15 เซนติเมตร ประกอบด้วยหน้าปก (หน้า 127) 1 แผ่น, วิธีการทานยา หน้า 128 จำนวน 4 หน้า และ แบบเก็บข้อมูลความผิดปกติของผู้ป่วยลมชัก หน้า 129 จำนวน 10 หน้า)

วันที่	ยาที่ใช้	เช้า	กลางวัน	เย็น	ก่อนนอน
_____	.....	☐	☐	☐	☐
_____	.....	■	■	■	■
_____	.....	☐	☐	☐	☐
_____	.....	■	■	■	■
_____	.....	☐	☐	☐	☐
_____	.....	■	■	■	■

แบบเก็บข้อมูลความผิดปกติของผู้ป่วยในคลินิกโรคลมชัก

วันที่	ความผิดปกติที่พบ

Appendix VI

Hospital Anxiety and Depression Scale ฉบับภาษาไทย (Thai HADS)

(Reference from http://go.to/ramamental)

อารมณ์ความรู้สึกเป็นส่วนสำคัญส่วนหนึ่งของการเจ็บป่วย ถ้าผู้ดูแลรักษาผู้ป่วยเข้าใจสภาพอารมณ์ความรู้สึกเหล่านี้ของท่าน ก็จะสามารถให้การช่วยเหลือ และดูแลท่านได้ดียิ่งขึ้น แบบสอบถามชุดนี้มีจุดมุ่งหมายที่จะช่วยให้ผู้ดูแลรักษาท่าน เข้าใจอารมณ์ความรู้สึกของท่านในขณะเจ็บป่วยได้ดีขึ้น กรุณาอ่านข้อความแต่ละข้อ และทำเครื่องหมายถูกในช่องคำตอบที่ใกล้เคียงกับความรู้สึกของท่าน **ในช่วง 1 สัปดาห์ที่ผ่านมา** มากที่สุด **และกรุณาตอบทุกข้อ**

คะแนน

1. ฉันรู้สึกตึงเครียด

(…..) เป็นส่วนใหญ่ 3

(…..) บ่อยครั้ง 2

(…..) เป็นบางครั้ง 1

(…..) ไม่เป็นเลย 0

2. ฉันรู้สึกเพลิดเพลินใจกับสิ่งต่างๆ ที่ฉันเคยชอบ

(…..) เหมือนเดิม 0

(…..) ไม่มากเท่าแต่ก่อน 1

(…..) มีเพียงเล็กน้อย 2

(…..) เกือบไม่มีเลย 3

3. ฉันมีความรู้สึกกลัว คล้ายกับว่ากำลังจะมีเรื่องไม่ดีเกิดขึ้น

(…..) มี และค่อนข้างรุนแรงด้วย 3

(…..) มี แต่ไม่มากนัก 2

(…..) มี เพียงเล็กน้อย และไม่ทำให้กังวลใจ 1

(…..) ไม่มีเลย 0

คะแนน

4. ฉันสามารถหัวเราะและมีอารมณ์ขันในเรื่องต่างๆ ได้

(…..) เหมือนเดิม 0

(…..) ไม่มากนัก 1

(…..) มีน้อย 2

(…..) ไม่มีเลย 3

5. ฉันมีความคิดวิตกกังวล

(…..) เป็นส่วนใหญ่ 3

(…..) บ่อยครั้ง 2

(…..) เป็นบางครั้ง แต่ไม่บ่อย 1

(…..) นานๆ ครั้ง 0

6. ฉันรู้สึกแจ่มใสเบิกบาน

(…..) ไม่มีเลย 3

(…..) ไม่บ่อยนัก 2

(…..) เป็นบางครั้ง 1

(…..) เป็นส่วนใหญ่ 0

7. ฉันสามารถทำตัวตามสบาย และรู้สึกผ่านคลาย

(…..) ได้ดีมาก 0

(…..) ได้โดยทั่วไป 1

(…..) ไม่บ่อยนัก 2

(…..) ไม่ได้เลย 3

คะแนน

8. ฉันรู้สึกว่าตัวเองคิดอะไร ทำอะไร เชื่องช้าลงกว่าเดิม

(…..) เกือบตลอดเวลา 3

(…..) บ่อยมาก 2

(…..) เป็นบางครั้ง 1

(…..) ไม่เป็นเลย 0

9. ฉันรู้สึกไม่สบายใจ จนทำให้ปั่นป่วนในท้อง

(…..) ไม่เป็นเลย 0

(…..) เป็นบางครั้ง 1

(…..) ค่อนข้างบ่อย 2

(…..) บ่อยมาก 3

10. ฉันปล่อยเนื้อปล่อยตัว ไม่สนใจตนเอง

(…..) ใช่ 3

(…..) ไม่ค่อยใส่ใจเท่าที่ควร 2

(…..) ใส่ใจน้อยกว่าแต่ก่อน 1

(…..) ยังใส่ใจตนเองเหมือนเดิม 0

11. ฉันรู้สึกกระสับกระส่าย เหมือนกับจะอยู่นิ่งๆ ไม่ได้

(…..) เป็นมากทีเดียว 3

(…..) ค่อนข้างมาก 2

(…..) ไม่มากนัก 1

(…..) เป็นส่วนใหญ่ 0

คะแนน

12. ฉันมองสิ่งต่างๆ ในอนาคต ด้วยความเบิกบานใจ

(…..) มากเท่าที่เคยเป็น 0

(…..) ค่อนข้างน้อยกว่าที่เคยเป็น 1

(…..) น้อยกว่าที่เคยเป็น 2

(…..) เกือบจะไม่มีเลย 3

13. ฉันรู้สึกผวาหรือตกใจขึ้นมาอย่างกระทันหัน

(…..) บ่อยมาก 3

(…..) ค่อนข้างมาก 2

(…..) ไม่บ่อยนัก 1

(…..) ไม่มีเลย 0

14. ฉันรู้สึกเพลิดเพลินไปกับการอ่านหนังสือ ฟังวิทยุ หรือโทรทัศน์ หรือกิจกรรมอื่นๆ ที่เคยเพลิดเพลินได้

(…..) เป็นส่วนใหญ่ 0

(…..) เป็นบางครั้ง 1

(…..) ไม่บ่อยครั้ง 2

(…..) น้อยมาก 3

การคิดคะแนน

อาการวิตกกังวล คิดคะแนนข้อคี่ทั้งหมด (1,3,5,7,9,11,13) รวมกัน

อาการซึมเศร้า คิดคะแนนข้อคู่ทั้งหมด (2,4,6,8,10,12,14) รวมกัน

Visual analog scale of antihistamine or sedative/hypnotic drugs

(ผู้วิจัยสร้างขึ้นเอง)

5	4	3	2	1	0
ง่วงมากที่สุด	ง่วงมาก	ง่วงปานกลาง	ง่วงน้อย	ง่วงน้อยมาก	ไม่ง่วง

Visual analog scale of antianalgesic drugs

(ผู้วิจัยสร้างขึ้นเอง)

5	4	3	2	1	0
ปวดมากที่สุด	ปวดมาก	ปวดปานกลาง	ปวดน้อย	ปวดน้อยมาก	ไม่ปวด

Appendix VII

- Syva® S-III Spectrophotometer for detecting blood levels of carbamazepine, phenytoin, and phenobarbital

Setting Wavelength: 340 nm

Con Cal: Amplification factor of 2.667

Temperature: 30°C

Sample time: 3-5 (adjust setting to allow complete aspiration of reaction mixture)

Vacuum:Autocarousel™ system:10-12 in.Hg (250-200mmHg)

Manual procedure: 5-8 in.Hg (125-200mmHg)

Materials provided

Emit®Phenytoin Assay Kit, when prepared, contains:

Reagent A (6.0ml)

Reagent B (6.0ml)

Drug Assay Buffer Solution (200ml)

Materials Required but Not provided

Emit® Antiepileptic Drug calibrators 0,1,2,3,4,5 (six 3.0 ml vials)

Controls

Class A volumetric pipettes

Distilled or deionized water

Syva® Flow Cell Cleaning Solutions A and B

Labolatory tissues (Kimwipes®, Kimberly-Clark)

Graduated container, accuracy within 1% of volume

The procedure for performing the Emit® Phenytoin Assay manually on Syva® Lab System is described below.

Procedure Setup

1. Prepare samples and reagents. Prepare all reagents according to the directions (see below). Allow all reagents, samples, and materials to reach room temperature of 20-25°C. Swirl the contents of all containers to mix reagents thoroughly just before use.

2. Check instruments setting. Ensure that the settings for wavelength, temperature, sample volume, and vacuum are adjusted correctly.

3. Ensure spectrophotometer is zeroed and amplication factor is correct.

4. Prime pipetter-diluter. Prime the pipetter-diluter with the buffer solution, being certain that there are no air bubbles in the lines.

5. Set up Breakers. Set up enough breakers in the work rack.

Assay Sequence

1. Dilute sample. Using the pipetter-diluter, aspirate 50 μg of calibrator, of the diluted sample and deliver this plus 250 μl of buffer solution into a second 2.0 ml disposable.

2. Dilute sample sgain. Using the pipetter-diluter, aspirate 50 μl of the diluted sample and deliver this plus 250 μl of buffer, solution to a second 2.0 ml breaker.

3. Add reagent A. Using the pipetter-diluter, aspirate 50 μl of reagent A and deliver this plus 250 μl of buffer solution to the second breaker.

4. Add reagent B. Using the pipetter-diluter, aspirate 50 μl of reagent B and deliver this plus 250 μl of buffer solution to the second breaker.

5. Aspirate into flow cell. Immediately upon addition of reagent B, aspirate the contents of the breaker into the spectrophotometer flow cell. This automatically activates the printer to time and record the measurement. After a 15 second delay, the spectrophotometer reads the absorbance of each sample. The change in absorbance over a 30-second measurement period is then used to calculate results.

6. remaining samples. Immediately upon aspiration, repeat step 1 through 6 for each calibrator, control, and sample to be assayed.

Calibration

Prepare a new standard curve whenever a new set of reagents is used and recalibrate as indicated by control results. The calibration sequence is 0,1,2,3,4,5. If a new bottles is used, validate the system by running controls.

Quality control

Validate the standard curve by assaying controls. Ensure that control results fall within acceptable limits as defined by your own laboratory. Once the standard curve is validated, run the samples.

Diluting High Concentration Samples

Patient samples containing more than 30 µg/ml (119 µmol/l) phenytoin may be diluted either manually or with the Syva® Pipetter-Diluter. When diluting patient samples, use Emit® Antiepileptic drug Calibrator 0.

Dilution with the Syva® pipetter-diluter.

1. Using the pipetter-diluter, aspirate 50 µl of sample and deliver this plus 250 µl of the buffer solution into a 2.0 ml disposable breaker.
2. Using the pipetter-diluter, aspirate 50 µl of Emit® Antiepileptic drug Calibrator 0 and deliver this plus 250 µl of buffer solution into the same breaker.
3. Use this diluted sample to start step 2 in the "Assay Sequence" procedure
4. Multiply the concentration result by 2 to obtain the original sample concentration.

For detecting blood levels of carbamazepine, valproate, clonazepam and phenobarbital, procedure has been performed like Phenytoin, but different in reagent, calibrators and buffer.

- Calibrator reagents
  - Carbamazepine calibrator
  - Phenytoin calibrator
  - Phenobarbital calibrator
  - Clonazepam calibrator
  - Valproate calibrator

Operating procedures of Syva® S-III Spectrophotometer

Preliminary operation

Perform the following procedure when initializing the instrument or when changing the viscosity of samples. When the instrument remains idle for a period of time, adjust the absorbance control for reading of approximately 3,000 A, this will reduce the voltage to the tungsten lamp, thus extending its life.

1. Turn instrument power on, allow approximately 15 minutes warm-up.
2. Turn vacuum pump switch to the ON position.

3. Adjust the vacuum and sample time to aspirate a volume which yields the best reproducibility. When uncertain of the amount of vacuum and sample time, begin with a vacuum of 10 to 12 inches Hg and a sample time setting of 3 or 4.

Measuring absorbance

After completing preliminary operation, measure absorbance as follow:

1. Position the CON-ABS-ACC control switch
2. Select the desired wavelength by turning the wavelength by turning the wavelength control knob while monitoring the wavelength indicator.
3. Fully depress the sample actuator bar for at least 5 seconds to purge the system with air.
4. Aspirate a reference sample by depressing the sample actuator bar to the first position.
5. Adjust the zero control knob, for a displayed reading of 0.000
6. Fully depress the sample actuator bar for at least 5 seconds to purge the sample with air.
7. Aspirate the sample and read the absorbance. Insure sample inlet tubing is well below the surface of the sample material without touching the bottom of the container when aspirating.

Measuring concentration

After completing the preliminary operation procedure, measure concentration as follow:

1. Position the CON-ABS-ACC control switch to CON.
2. Select the desired wavelength by turning the wavelength control knob, while monitoring the wavelength indicator.
3. Fully depress the sample actuator bar for at least 5 seconds to purge the system with air.
4. Aspirate a reference sample by depressing the sample actuator bar to the first position.
5. Adjust the zero control knob, for a displayed reading of 0.000
6. Fully depress the sample actuator bar for at least 5 seconds to purge the sample with air.
7. Aspirate the sample and read the absorbance. Insure sample inlet tubing is well below the surface of the sample material without touching the bottom of the container when aspirating.
8. Adjust the CON. CAL. control, for a digital readout corresponding to the known concentration. For example, if the concentration of a known sample is 20 gm/100ml, adjust the concentration calibration control for 2000 or 0200.
9. Position the decimal point control to indicate the desired units, for example, 20.00 or 020.0.

10. Fully depress the sample actuator bar for at least 5 seconds to purge the system with air.
11. Aspirate a sample and read the concentration. The concentration of the sample will be displayed directly in grams/100 ml.
12. Fully depress the sample actuator bar for at least 5 seconds to purge the system with air.
13. Repeat steps 11 and 12 for subsequent measurements of like samples. Always introduce the reference blank and zero the instrument after changing wavelenghts or reagents.
14. Perform the End-of-Run Cleaning procedure.

VITAE

Miss sermsook jantai was born on the 25th April 1973 at Rajchavitee Hospital, Bangkok. She graduated Bachelor degree in Pharmaceutical Sciences in 1996 from Faculty of Pharmaceutical Sciences, Khon Kaen University. Her current position is a pharmacist at Pharmacy department, Prasat Neurological Institute, Bangkok.