การใช้ยาออกซคาร์บาซีปีนเป็นยาเสริมในผู้ป่วยลมชักชาวไทยที่มีอาการชักบางส่วน
ซึ่งไม่สามารถควบคุมได้ด้วยยากันชักที่ใช้อยู่

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OXCARBAZEPINE AS ADD-ON THERAPY IN THAI EPILEPTIC PATIENTS WITH REFRACTORY PARTIAL SEIZURES

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การวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาประสิทธิภาพและความปลอดภัยของยาออกซคาร์บาซีปีนขนาด 600 และ 1200มก./วัน ในผู้ป่วยโรคลมชักชาวไทยที่มีอาการชักชนิดบางส่วนซึ่งไม่สามารถควบคุมอาการชักได้ด้วยยากันชักที่ใช้อยู่โดยศึกษาในรูปแบบของการใช้ยาออกซ์คาร์บาซีปีนเป็นยาเสริมร่วมกับยากันชักชนิดอื่นที่ผู้ป่วยใช้อยู่เดิม และเพื่อศึกษาถึงความสัมพันธ์ระหว่างระดับ MHD ซึ่งเป็นเมแทบอไลต์ที่แสดงฤทธิ์ต้านชักของยาออกซคาร์บาซีปีน, กับผลทางการรักษา

ผู้ป่วยซึ่งไม่สามารถควบคุมอาการชักชนิดบางส่วนซึ่งรวมถึงอาการชักชนิดบางส่วนที่จะกลายเป็นการชักทั้งตัวในขั้นต่อไปจำนวน 39 คนมีอายุระหว่าง 15-65 ปี ถูกประเมินในการศึกษาแบบสุ่ม, ปิดบังทั้งสองด้าน โดยแบ่งการศึกษาออกเป็น 3 ระยะ คือ : 1) ระยะพื้นฐาน, ศึกษาข้อมูลของการชัก (ชนิดและความถี่) ขณะที่รักษาด้วยยาเดิม (56 วัน); 2) ระยะให้การรักษาแบบปิดบังทั้ง 2 ด้าน, ผู้ป่วยได้รับยาออกซ์คาร์บาซีปีน(ขนาด 600 หรือ 1200มก./ วัน) ร่วมกับยากันชักเดิมที่ได้รับในระยะพื้นฐาน (98 วัน); 3) ระยะเปิดเผยขนาดของยาออกซ์คาร์บาซีปีนที่ผู้ป่วยได้รับ โดยผลการศึกษาจะถูกประเมินถึงสิ้นสุดระยะที่ให้การรักษาแบบปิดบังทั้ง 2 ด้าน ตัวแปรที่แสดงถึงประสิทธิภาพขั้นปฐมภูมิและทุติยภูมิคือ ค่าเฉลี่ยเปอร์เซนต์การเปลี่ยนแปลงความถี่ของการชักภายใน 28 วันเมื่อเทียบกับระยะก่อนใช้ยา และเปอร์เซนต์ของผู้ที่มีความถี่ของการชักลดลงอย่างน้อย 50%, ตามลำดับ ผลการศึกษาพบว่าค่ามัธยฐานเปอร์เซนต์ความถี่ของการชักที่ลดลงเท่ากับ 47% และ 58% ในกลุ่มของผู้ได้รับยาในขนาด 600 และ 1200มก./ วัน ตามลำดับ, และพบว่าผู้ป่วยที่มีความถี่ของการชักลดลงอย่างน้อย 50% เท่ากับ 44% และ 53% ในกลุ่มที่ได้รับยาขนาด 600 และ 1200 มก./ วัน ตามลำดับ โดยทั้ง2ตัวแปรดังกล่าวไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างผู้ป่วย2กลุ่ม($p>0.05$) นอกจากนั้นยังพบว่าค่าเฉลี่ยความเข้มข้นของระดับ MHD ในพลาสมามีความสัมพันธ์กับขนาดของยาที่ได้รับ($p=0.000$) ระหว่างได้รับยาออกซ์คาร์บาซีปีนมีผู้ป่วย 85%และ 84% ในกลุ่ม 600 และ 1200มก./ วันตามลำดับที่รายงานอาการไม่พึงประสงค์อย่างน้อย1ชนิด ซึ่งอาการดังกล่าวมักเกิดขึ้นชั่วคราวและมีความรุนแรงเล็กน้อยถึงปานกลาง อาการไม่พึงประสงค์ที่พบได้บ่อยทั่วไป คือ อาการที่มีความสัมพันธ์กับระบบประสาทส่วนกลาง ผลการศึกษาแสดงให้เห็นว่ายาออกซ์คาร์บาซีปีนทั้ง 2ขนาดมีประสิทธิภาพและความปลอดภัยในผู้ป่วยโรคลมชักชาวไทยซึ่งไม่สามารถควบคุมการชักได้เมื่อใช้ในรูปแบบของการเป็นยาเสริมร่วมกับยากันชักตัวอื่นและประสิทธิภาพของยามีแนวโน้มเพิ่มขึ้นตามขนาดยา

ภาควิชา เภสัชวิทยา	ลายมือชื่อนิสิต……..
สาขาวิชา เภสัชวิทยา	ลายมือชื่ออาจารย์ที่ปรึกษา……
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MISS PETISARA KRAIPRAB: OXCARBAZEPINE AS ADD-ON THERAPY IN THAI EPILEPTIC PATIENTS WITH REFRACTORY PARTIAL SEIZURES. THESIS ADVISOR: ASSOC. PROF. MAYUREE TANTISIRA, Ph.D., THESIS COADVISOR: Lt. COL. Dr. YOTIN CHINVARUN, MD. Ph.D.,[136] pp. ISBN 974-17-5372-1.

The purposes of the present study were to evaluate the efficacy and safety of oxcarbazepine(OXC) in the dosage of 600 and 1200 mg/d as add-on therapy in Thai epileptic patients with uncontrolled partial seizures and to explore therapeutically relevant plasma concentration of 10-monohydroxy derivative; MHD which responsible for the pharmacologic effect of OXC.

A total of 39 patients aged 15-65 years with uncontrolled partial seizures with or without secondarily generalized seizures were evaluated in a randomized, double-blind trial consisting of three phases: 1) a 56-day baseline phase (patients maintained on their current anti-epileptic drugs); 2) a 98-day double-blind treatment phase (OXC either 600 or 1200mg/d orally was added); 3) an open-label extension phase. Data are reported only from the double-blind period; the open-label extension phase is ongoing. The primary efficacy variable was percentage change in seizure frequency per 28 days relative to baseline and the secondary efficacy was treatment responder. The results showed that the median reduction in seizure frequency were 47% and 58% for patients receiving 600,1200 mg/d respectively. Of patients in the 600 and 1200 mg/d OXC group, 44% and 53% respectively, had more than 50% reduction in seizure frequency. No significant differences were found between two treatment groups ($p>0.05$) in both efficacy variables. Mean trough plasma concentrations of MHD were correlated with OXC dosage ($p=0.000$). During double-blind treatment phase, 85%and 84% of patients receiving 600 and 1200mg/d OXC, respectively, reported one or more adverse events (AEs) with mild to moderate degree, transient in nature. The most common AEs were related to the central nervous systems. In conclusion, OXC both dosage of 600 and 1200 mg/d as add-on therapy is effective and safe in Thai epileptic patients with uncontrolled partial seizures. The effectiveness of OXC seemed to be increased with increasing dosage.

Department Pharmacology Student's signature……..

Field of study Pharmacology Advisor's signature……...

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

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LIST OF ABBREVIATIONS

%	= percent
%RSD	= % relative standard deviation
α	= alpha
°C	= degree Celcius
μg	= microgram
μL	= microliter
γ	= gamma
5-HT	= 5-hydroxytryptamine acid
AE	= adverse effect
AED	= anti-epileptic drug
ALP	= alkaline phosphatase
AMPA	= alpha-amino-3-hydroxy-5-methyl- isoxyzole-4-propionic
ATPase	= adenosine-tri-phosphatase
AUC	= area under the curve
BUN	= blood urea nitrogen
BZP	= benzodiazepine
Ca^{2+}	= calcium ion
CBZ	= carbamazepine
Cmax	= maximum concentration
Cmin	= minimum concentration
CNS	= central nervous system
Conc.	= concentration
CrCl	= creatinine clearance
CYP	= cytochrome P450
d	= day
e.g.	= exampli gratia (for example)

LIST OF ABBREVIATIONS (CONTINUED)

EEG	= electroencephalogram
ESM	= ethosuximide
et al.	= et alii (and other)
FBM	= felbamate
FBS	= fasting blood sugar
GABA	= gamma-amino butyric acid
GBP	= gabapentin
HPLC	= high-performance liquid chromatography
hr	= hour
i.e.	= id est (that is)
ILAE	= International League Against Epilepsy
JME	= juvenile myoclonic epilepsy
K^+	= potassium ion
KA	= kainic acid
kg	= kilogram
L	= liter
LOD	= limit of detection
LOQ	= limit of quantification
LTG	= lamotrigine
M^2	= square meter
mEq	= milliequivalent
mg	= milligram
mGluR	= metabotropic glutamate recepter
MHD	= monohydroxy derivative
min	= minute
mL	= milliliter
mm	= millimeter

LIST OF ABBREVIATIONS (CONTINUED)

mmol	= millimole
Na^+	= sodium ion
ng	= nanogram
nm	= nanometer
NMDA	= N-methyl-D-aspatate
nmol	= nanomole
OXC	= oxcarbazepine
PB	= phenobarbital
PCH	= percentage change
PHT	= phenytoin
SD	= standard deviation
SGOT	= serum glutamic oxaloacetic transaminase
SGPT	= serum glutamate pyruvate transaminase
TGB	= tiagabine
TPM	= topiramate
U.S.A.	= the United States of America
UDP	= uridine diphosphate
VGB	= vigabatrin
VPA	= valproic acid
wk	= week
ZNM	= zonisamide

CHAPTER I

INTRODUCTION

Background and Rationale

Monotherapy with antiepileptic drugs (AEDs) has been advocated as the preferred regimen for patients with epilepsy (Beydoun, 1997), albeit, it has been shown that AED monotherapy resulted in total seizure control in only 39% of the trial population after 1 year (Mattson et al., 1985). Adjunctive therapy offers the possibility of increased seizure control but drug interactions and toxicity are often problematic (Patsalos and Sander, 1994). Some newer AEDs have minimal drug-drug interaction but they are also of marginal efficacy during adjunctive therapy as well (Mattson, 1992).

Oxcarbazepine (10,11-dihydro-10-oxo-5*H*-dibenz[*b,f*]azepine-5 carboxamide; GP 47680; OXC) is an antiepileptic drug currently approved in most countries worldwide as monotherapy and adjunctive therapy for the treatment of partial seizures with or without secondarily generalized seizures, as well as generalized tonic–clonic seizures in adult and children.

OXC is structurally related to carbamazepine (CBZ), with a similar spectrum of activity and anticonvulsant efficacy in animal models of seizures. However, unlike standard AEDs (e.g., CBZ, phenytoin (PHT), and valproic acid (VPA)) which undergo oxidative metabolism, OXC is extensively and rapidly metabolized by reduction to 10-monohydroxy derivative (10,11-dihydro-10hydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide [MHD]; GP 4779) which is likely to be the major active component responsible for the phamacologic effect of OXC (Grant and Faulds, 1992). As a result, OXC has an extremely low potential for the induction of hepatic enzymes, and a low propensity for drug-drug interactions. In an in vitro study, OXC and MHD were shown to

have a low potential to inhibit the major human cytochrome P450 (CYP450) enzymes responsible for the metabolism of other drugs, with the exception of CYP2C19, which metabolizes drug such as phenobarbital (PB) and PHT (Tripp et al., 1996). Similar result has been observed in clinical study, therefore interactions could arise when coadministering high dose of OXC with PB or PHT.

Previous clinical experience with OXC indicates that OXC has an efficacy spectrum similar to that of PHT (Bill et al., 1997; Guerreiro et al., 1997), VPA (Christe et al., 1997) and CBZ (Dam et al., 1989) but may have advantage in tolerability and clinical usefulness. OXC has demonstrated efficacy as monotherapy in presurgical hospitalized patients with refractory partial seizures (Schachter et al., 1999) and as adjunctive therapy in adults (Barcs et al., 2000) and children (Glauser et al., 2000). Therapeutic effects in monotherpy and adjunctive therapy were seen at dosages between 600 and 2400 mg/d.

In Thailand, OXC was registered as a new antiepileptic drug under the name "Trileptal®" in 2001. By the Safety Monitoring Program scheme, OXC will be exclusively available in hospitals until the status of new drug is removed by evidence proving of its efficacy and safety in Thai patients. Until now there is no appreciable information on such data, therefore we consider it interesting to evaluate the efficacy and safety of OXC as adjunctive therapy in Thai patients whose partial seizures were not adequately controlled by currently used AEDs. A randomized, double-blind, dose-controlled study design was used to compare between two oral OXC dosages (600 and 1200 mg/d, administered in divided doses twice daily). Plasma MHD was determined to explored therapeutic range and their relationship to safety and efficacy.

Hypothesis

As add-on therapy in refractory epileptic patients, 600 mg/d OXC group is less effective than 1200 mg/d OXC.

Objective

1. To evaluate the safety and efficacy of OXC between two oral dosages (600 and 1200 mg/day) as add-on therapy in Thai-patients with inadequately controlled partial seizures.
2. To explore therapeutically relevant plasma concentration of MHD.

Expected outcome

1. Information of the safety and efficacy of OXC as adjunctive therapy in Thai epileptic patients with refractory partial seizure.
2. Therapeutic trough plasma of MHD in relation to the efficacy and safety of OXC as add-on therapy.

CHAPTER II

LITERATURE REVIEW

Epilepsy

Epilepsy is a group of disorders characterized by excessive and paroxysmal neural discharges causing sudden alteration in neurologic function. The terms “epilepsy” and “seizure” refer to similar clinical conditions; however, epilepsy refers to the spontaneous recurrent seizures. Seizures are behavioral changes that result from abnormal paroxysmal neuronal discharge or the clinical manifestation of abnormally hyperexcitable cortical neurons and are a symptom of an underlying brain problem (Adams, 1997). The behavioral manifestations of a seizure are determined by the normal functions of the region of cortex in which neurons fire abnormally (McNamara, 1999).

All people are capable of experiencing seizure. Brain insults such as fever, hypoglycemia, hyponatremia, and extreme acidosis or alkalosis can trigger a seizure, but if the condition is corrected, seizure do not recur (Stringer, 1998). Precipitating factors for seizures including fever, sleep deprivation, menstruation, hyperventilation, emotional stress, and exposure to flashing lights (photic stress) as occurs with video games. Whereas all patients with epilepsy have seizures, many more patients have a single seizure during life and are not considered to have epilepsy (Foldvary, 2000).

Epilepsy affects many aspects of life such as self-esteem, interpersonal relationships, and obtaining and maintaining employment. In addition epileptic seizures often cause transient impairment of consciousness, leaving the individual at risk of bodily harm and often interfering with education (Mcnamara, 1996; stringer, 1998).

Epilepsy is the third most common neurological disorder, following stroke and Alzheimer's disease, affecting 50 million people worldwide (Fisher, 1998). It was estimated that epilepsy affects 2.3 million Americans of all ages, approximately 181,000 new cases of seizure and epilepsy occur each year (William, 2000). About 10% of the United states population will experience one seizure in lifetime, and 3% will develop epilepsy by age of 75 (Hauser et. al, 1996). The onset of new seizure may begin at any time in life; there is bimodal distribution, with the highest frequencies in newborns and infants, and in people older than 65 years. The frequency is higher in patients who have additional insults to the brain, such as mental retardation, trauma, or Alzheimer's disease (William, 2000).

In a majority of patients, seizures have a focal onset and approximately 30% of the seizure begin in the temporal lobe (Meldrum, 1995). A majority of the patients (about 70%) with diagnoses of epilepsy soon go into remission, but for the remainder, the condition will become chronic and in some of these patients seizures are resistant to drug therapy. In particular, complex partial seizures are usually refractory to antiepileptic drug (AED) therapy, carry a worse prognosis, and require higher AED blood level than of generalized seizures.

Etiology

Seizures can be resulted from either primary central nervous system dysfunction or an underlying metabolic derangement or systemic disease. This distinction is critical, since therapy must be directed at the underlying disorder as well as at seizure control. A list of common neurologic and systemic disorders that induce seizures is presented in Table 1. In addition drug withdrawal or drug over dose may result in seizure as well (Table 2) (David et al., 2002). The age of the patients may help in establishing the cause of seizures (Table 3) (Paul, 2001).

Table 1. Common causes of seizures of new onset (David et al., 2002).

Primary neurologic disorders
Benign febrile convulsions of childhood
Idiopathic epilepsy
Head trauma
Stroke or vascular malformations
Mass lesions
Meningitis or encephalitis
HIV encephalopathy
Systemic disorders
Hypoglycemia
Hyponatremia
Hyperosmolar states
Hypocalcemia
Uremia
Hepatic encephalopathy
Porphyria
Drug overdose
Drug withdrawal
Global cerebral ischemia
Hypertensive encephalopathy
Eclampsia
Hyperthermia

Table 2. Major categories of drugs reported to cause seizures (David et al., 2002).

Anticholinesterased (organophosphated, physostigmine)
Antidepressants (tricyclic, monocyclic, heterocyclic)
Antihistamines
Antipsychotics (phenothiazines, butyrophenones, clozapine
B-Adrenergic receptor blockers (propranolol, oxprenolol)
Chemotherapeutics (etoposide, ifosfarmide, cisplatinum)
Cyclosporine, FK 506
Hypoglycemic agents (including insulin)
Hypoosmolar parenteral solutions
Isoniazid
Local anesthetics (bypivacaine, lidocaine, procaine, etidocaine)
Methylxanthines (theophyline, aminophylline)
Narcotic analgesics (fentanyl, meperidine, pentazocine, propoxyphene)
Penicillins
Phencyclidine
Sympathominetics (amphetamines, cocaine, ephedrine, MDMA[1]
"ecstasy", phenylpropanolamine, terbutaline)

[1]Methylenedioxymethamphetamine.

Table 3. Common causes of seizures by age (Paul, 2001).

NEONATE TO 3 YR	3-20 YR	20-60 YR	OVER 60 YR
Prenatal injury	Genetic predisposition	Brain tumors	Vascular disease
Perinatal injury	Infections	Trauma	Brain tumors, especially metastatic tumors
Metabolic defects	Trauma	Vascular disease	Trauma
Cogenital malformations	Cogenital malfomations	Infections	Systemic metabolic derangements
CNS Infections	Metabolic defects		Infections
Postnatal trauma			

Epileptogenesis

Epileptogenesis is thought of as a cascade of dynamic biological events altering the balance between excitation and inhibition in neural network (Clark and Wilson, 1999). The term applies to any of the progressive biochemical, anatomic, and physiologic changes leading up to recurrent seizures. Proposed mechanism of epileptogenesis must in corporate information from levels of organization that range from molecular (e.g., altered gene expression) to macrostructural alteration (e.g., altered neural networks) (Lowenstein, 1996).

Neuroanatomy pertaining to seizure and epilepsy

The neocortex (cortical area covering surface of brain), hippocampus, and other mesial temporal frontal areas are frequent sites of seizure onset. Subcortical areas, such as the thalamus, substantia nigra, and corpus striatum, are thought to play key role in the spread of seizure activity and generation of generalized seizures. In the “normal” brain, inhibitory stimuli from these subcortical areas modulate excitatory neurotransmission between the cortex and other brain areas, and limit the spread of abnormal electrical signals. Depression of the inhibitory activity of these areas in the brains of patients with epilepsy may facilitate the spread of seizure activity following an initial partial seizure or the generation of primary generalized seizures (Fisher, 1998).

Neurophysiological aspect of epileptogenesis

When the presynaptic axon terminal is stimulated by an action potential, there is an influx of Ca^{2+} triggering the release of neurotransmitters that bind to postsynaptic membrane receptors. This process produces excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) whose summation and synchronization comprise the electrical activity recorded from the surface electroencephalogram (EEG). Two essential physiologic elements each represent the net effect of many complex, interacting processes. The first is an abnormality of cellular excitability, which might be termed “neuronal deregulation”, arising from mechanisms that affect membrane depolarization and repolarization. The second is a “network defect” which derives from mechanism

underlying the development of aberrant neuronal integration, abnormal synchronization of neuronal populations, and propagation of the epileptic discharge within neural pathways. Both sets of disturbances must be present before a seizure can occur (Jerome and Pedley, 1997).

Biochemical aspect of epileptogenesis

Epileptic seizures occur as a result of imbalance between inhibitory and excitatory neurotransmitter system, although the exact mechanisms underlying this imbalance remain uncertain (Meldrum,1995; Holmes, 1997). Proposed mechanisms for the generation and spread of seizure activity within the brain include abnormalities in the membrane properties of neurons, changes in the ionic micro environment surrounding the neuron, decreased inhibitory neurotransmission which is primarily by gamma-amino butyric acid (GABA), or enhanced excitatory neurotransmission which are primarily mediated by the acidic amino acid, glutamate and aspatate (Fisher, 1998).

Loss of GABA has long topped the list of potential epileptogenic factors. In addition, enhanced glutamatergic excitation is another potential epileptogenic mechanism that has received much attention in recent years, paticularly with respect to the role of the N-methyl-D-aspartate (NMDA) type glutamate receptor which mediated activity appears to contribute synaptic drive associated with epileptiform events (Schwartzkroin, 1997).

Genetic aspect of epileptogenesis

Recent advances indicate that some cellular or molecular mechanisms might be common to distinct forms of epilepsy. Progress in molecular genetics has advanced understanding of the molecular etiology of genetic diseases. Discoveries have pinpointed mutation of genes encoding voltage-and ligand-gated ion channels of neurons as the etiology of some forms of human epilepsy, thereby implicating alterations of intrinsic properties and/or synaptic function as the principal causal factors (McNamara 1999).

Genetic causes contribute to a diversity of human epilepsies. They are responsible for some rare forms inherited in a mendelian pattern (for example, autosomal dominant or autosomal recessive), and are solely or mainly responsible for some common forms such as juvenile myoclonic epilepsy (JME) or childhood absence epilepsy (CME). In contrast to the rare forms caused by single mutant gene, JME and CME are almost certainly due to inheritance of or more susceptibility genes. Genetic determinants may also contribute some degree of risk to epilepsies caused by damage to the cerebral cortex, but the magnitude of this risk is much less than, for example, with JME (McNamara 1999).

Because some of the genes for rare epilepsies encode defective ion channel proteins and thereby affect fundamental properties of neuron excitability-genetically based alterations in ion channel function may also underlie common epilepsy syndromes (McNamara 1999). Challenges are significant because of 1) genetic heterogeneity, i.e., different mutations at the same genetic locus, or mutations at different genetic loci, may give rise to indistinguishable epilepsy phenotypes; 2) phenotypic heterogeneity, i.e., the same mutation at a single locus can be modified by other genes to give rise to distinct phenotypes; 3) lack of any obvious functional relationship between the mutated gene and neuronal hyperexcitability (McNamara, 1999; Berkovic and Scheffer, 1999).

Biological aspect of epileptogenesis

Characterization of normal cortical development and its underlying molecular and cellular mechanisms have led to better understanding of cortical malformations and hypotheses of epileptogenesis. Cortical malformations, once considered rare, are now known to account for at least 15% of epilepsy in adults.

Developmental defects also may play a role in more common types of epilepsy. The recent finding of GABA and glutamate neurons arising from different regions within the developing telencephalon has generated hypotheses of epilepsy evolving from disrupted migration of discrete subpopulations of neurons (Jacob et al, 2001).

Classification of epileptic seizures and epilepsy syndromes

Many different types of seizures can be identified on the basis of their clinical phenomena. These clinical characteristics, along with electroencephaographic (EEG) features, can be used to categorize seizures (Commission, 1981). In 1964, The Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) proposed the first official classification of epileptic seizures, which was revised in 1981 (Commission, 1964; Commission, 1981).

The classification of epileptic seizures are summarized in Table 4. Based on this classification, epileptic seizures are fundamentally divided into two major groups: partial and generalized. Partial (focal, local) seizures are those in which clinical or electrographic evidence exists to suggest that the attacks have a localized onset in the brain, usually in a portion of one hemisphere, while generalized seizures are those in which evidence for a localized onset is lacking

In addition to classifying the seizures that occur in patients with epilepsy, epilepsy syndromes have been classified by the International League Against Epilepsy, similar to the classification of seizure characterized by different seizure types, EEG features, etiologies, ages of onset, family history, and prognosis (Commission, 1989). The most important groupings of epilepsy syndromes are localization-related epilepsies (or focal), in which the pathology is localized to one region of the brain, and generalized epilepsies, in which the pathology is expressed throughout the whole brain.

The etiology can be further subdivided into three categories; (1) those that are “symptomatic” of underlying brain disease, (2) “idiopathic” causes in which an identifiable lesion is never identified, and (3) “cryptogenic” causes in which an anatomic lesion is suspected to be present but cannot be identified. Idiopathic and cryptogenic usually mean unknown in medical terminology, but in the epilepsy syndromes, the idiopathic syndromes are thought to be due to inherited abnormalities of neurotransmission without any anatomic lesion, whereas the cryptogenic syndromes are

those that are actually symptomatic but the brain pathology cannot be identified with current technology (Fountain, 2000).

Table 4. Summary of the International Classification of Epileptic Seizures (Commission on Classification, 1981)

I. Partial (focal, local) seizures
A. Simple partial seizures (consciousness not impaired)
With motor symptoms
With somatosensory or special sensory symptoms
With autonomic symptoms
With psychic symptoms
B. Complex partial seizures (with impairment of consciousness)
B.1 Beginning as simple partial seizures and progressing to impairment of consciousness
With no other features[a]
With features as in A1-4[a]
With automatisms[a]
B.2 With impairment of consciousness at onset
With no other features[a]
With features as in A1-4[a]
With automatisms[a]
C. Partial seizures secondarily generalized[a]
II. Generalized seizures (convulsive or nonconvulsive)
Absence seizures[a]
Myoclonic seizures[a]
Clonic seizures[a]
Tonic seizures[a]
Tonic – clonic seizures[a]
Atonic seizures[a]
III. Unclassified epileptic seizures[a]

[a]Categories used in the comparisons.

Treatments of Epilepsy

Therapy should be directed toward the cause of the seizures, if known. Idiopathic epilepsy is treated with antiepileptic medications. Although AEDs are the mainstay of treatment, alternative treatment modalities have varying degrees of clinical and experimental support (David et al., 2002).

Non-Drug Treatments of Epilepsy

Lifestyle modifications

Lifestyle modifications, particularly avoidance of stimulants, alcohol and sleep deprivation, can be very important in certain syndromes and individuals. Relaxation, stress reduction, biofeedback, and other behavioral techniques can help a subset of patients, especially those with a reliable aura preceding complex partial or secondarily generalized seizure. Dietary supplements are of unproven value, except for pyridoxine (vitamin B6), which is crucial for treating rare pyridoxine dependency of neonates and infants and for seizures due to antituberculous therapy with isoniazid.

The ketogenic diet

The Ketogenic diet has been used for several decades in children with severe seizure disorders especially with multiple seizure types, and undergo something of a revival. It bases on the observation that ketosis and acidosis have anti-seizure effects. Because of risks of severe metabolic abnormalities during and after the initial fasting period, this diet initiated in the hospital. Strict protein, calorie, and especially carbohydrate restriction in the setting of a high fat diet is needed for ketosis, and may be difficult to maintain. In a minority of patients with intractable epilepsy, staying on this diet for months or years can result in a sustained improvement in seizure control, rarely even allowing withdrawal of AEDs.

The vagal nerve stimulation

The vagal nerve stimulator, a device that provides intermittent electrical stimulation of the left vagus nerve, was shown in several studies to be effective in

reducing the frequency of complex partial seizures, and received FDA approval in 1997. The stimulator is surgically implanted subcutaneously. Adverse effects include hoarseness, throat pain, or a feeling of dyspnea during stimulation; these are generally mild. The mechanism by which stimulation reduces seizures is not well established. The stimulator has been studies only in combination with AED treatment. The cost of the device and its implantation may be limiting factor.

Surgical Treatment of Epilepsy

Although the majority of patients with epilepsy achieve adequate control, about 20-30% of patients have drug resistant, intractable epilepsy that significantly impairs their quality of life. Patients such as these may benefit from a surgical evaluation (Trescher and Lesser, 2000). Surgical treatment is indicated in such patients if seizure arise from an area that can be removed without causing unacceptable neurological deficits. The goal of surgery is to eliminate or greatly reduce the frequency and intensity of seizures. Even patients whose seizures are relatively well controlled may be considered for surgery if there is certain characteristic lesions that strongly suggest such intervention can be curative.

Drug treatment of epilepsy

The goal of therapy with an AED is to keep the patient free of seizures without interfering with normal brain function as well as absence of disabling side effects (Mattson, 1995). No logical system has been devised to classify AEDs. One convenient method is to divide them into conventional, new, unconventional, and experiment categories. Conventional AEDs are those that were available before the onslaught of new AEDs that were approved starting in 1993. Although several conventional AEDs are available, only phenytoin(PHT), carbamazepine(CBZ), valproate(VPA), phenobarbatal(PB), and primidone are widely used. New AEDs are those that have been approved since 1993, include felbamate, gabapentin, lamotrigine, topiramate, tiagabine, zonisamide, levetiracetam, vigabatrin and oxcarbazepine. Commonly used AEDs and their dosages and methods of administration are listed in Table 5 (Fountain, 2002).

Selection of AEDs should be based on the epilepsy syndrome when it is known, but because the etiology is often unknown, the choice of an AED must be based solely on the type of seizures present (Table 6), (Paul, 2001; David et al., 2002). PHT, CBZ, or VPA are the current drugs of first choice for the treatment of generalized tonic-clonic or partial seizure in adults whereas VPA or CBZ is preferred for children. PB is also very effective in treating generalized tonic-clonic seizure in adults, but it is less helpful for treatment of complex partial seizures. Absence attacks of the petit mal variety are treated with VPA or ethosuximide. Myoclonic seizures are treated with VPA or clonazepam. In choosing a medication for a patient with several seizure types, it is best to select a drug that is effective for all types. However, therapy can also be directed toward the most dangerous seizure type or the seizure that most strongly affect quality of life or work. The drug should not exacerbate seizure that may occur in the patient's epilepsy syndrome (Devinsky and Cramer, 2000).

Table 5. Summary of anticonvulsant drug therapy (Fountain, 2002).

Drug	Usual *Preparation*	*Loading or* Initial Dose	Maintenance *Dose*	Serum Half-Life (Normal Renal and Hepatic Function)	Therapeutic Serum Levels	Indications[1]
Phenytoin (Dilantin)	100-mg capsule Also 30-mg Capsule, 50-mg tablet	Oral loading; 1000 mg in two to four divided doses over 12-24hours Intravenous loading; 1000-1500mg (15-18mg/kg) not exceeding 50 mg/min Fosphenytoin id prodrug form for intramuscular or intravenous use	300-400 mg/d in a single dose or divided doses	Oral: 18-24 hours Intravenous; 12 hours (kinetics are dose dependent and may vary widely)	10-20 ug/mL	P, G
Carbamazepine (Tegretol)	200,300 mg XR:100,200 400 mg	100 mg twice a day; increase by 200 mg/d to maintenance dose	400-1600 mg/d in three or four doses, or in two doses if XR form	12-18 hours monoyhrtspy	4 – 12 ug/mL	P, G
Oxcarbazepie (Trileptal)	150, 300, 600mg	300 mg twice a day	1200-2400 mg/d in two divided doses	8-10 hours	Not established	P
Phenobarbital (Luminal)	15, 30, 60, 100 mg	Oral loading; 180 mg twice a day for 3 days or same as maintenance	90-180 mg/d in a single dose	3-5 days	20-40 ug/mL	G
Valproic acid (Depakote, Depakene)	250 mg	Same as Maintenance dose	750-3000 mg/d in two or three doses	6-18 hours	50-150 ug/mL	G, M, A, P
Ethosuximide (Zarontin)	250-mg capsules	15 mg/kg/d, then increase by 25 mg/d at weekly intervals to maintenance dose	15-40 mg/kg/d in two or three doses	24-36 hours (children); 60 hours (adult)	40-100 ug/mL	A
Clonazepam (Klonopin)	0.5, 1, 2 mg	Children: 0.01-0.03 mg/kg/d in two or three doses Adults: 0.5 mg/d	Children: 0.01-0.02 mg/kg/d Adults; 1.5-2.0 mg/d; in or three divided doses	20-40 hours	0.02-0.10 ug/mL	A
Gabapentin (Neurontin)	100,300 mg	300 mg three times a day	900-4800 mg/d in three divided doses	5-7 hours	Not established	P,SG,Adj

Continued

Table 5. Summary of anticonvulsant drug therapy (continued).

Drug	Usual *Preparation*	*Loading or* Initial Dose	Maintenance *Dose*	Serum Half-Life (Normal Renal and Hepatic Function)	Therapeutic Serum Levels	Indications[1]
Lamotrigine (Lamictal)	50, 100, 200 mg	25 mg twice a day then show increase[2]	200-500 mg/d 100-700 in two doses[2]	24 hours 12-60 hours[2]	Not established	P,SG,Adj
Levetiracetam (Keppra)	250, 500 750 mg	250-500 twice a day	1000-3000 mg/d in two divided doses	8-10 hours	Not established	P,Adj
Vigabatrin (Sabril)	500 mg	500 mg twice a day; increase by 500 mg every week	2-4 g/d in two divided doses	5-8 hours	Not established	P,Adj
Topiramate (Topamax)	25, 100, 200 mg	25 mg/d; increase by 25-50 mg every 2 weeks	200-400 mg/d in two divided doses	16-30 hours	Not established	P,Adj
Tiagabine (Gabatril)	4, 12, 16, 20 mg	4 mg/d; increase by 4-8 mg every week	12-56 mg/d in three divided doses	5-13 hours	Not established	P,Adj
Zonisamide (Zonegran)	100 mg	100 mg/d	400-600 mg/d in one to two doses	52-69 hours	Not established	P,Adj

[1] A, absence; Adj, adjunctive; G, generalized tonic-clonic/ M, myoclonic, p, partia;. S, secondarily generalezed tonic-clonic

[2]Varies depending on interaction with coadministered anticonvulsant drugs; 25 mg every other day for 2 weeks when taking valproic acid; see Table 8-8.

[3]Not approved in the United States.

Table 6. First-and Second-Line Drugs for Specific Seizure Types (Pual, 2001).

	PARTIAL SEIZURES AND LOCALIZATION RELATED EPILEPSY	GENERALIZED SEIZURES			
		TONIC-CLONIC	*ABSENCE*	MYOCLONIC	ATONIC/TONIC
First-line drugs	Carbamazepine Phenytoin Lamotrigine Valproate Oxcarbazepine	Valproate Lamotrigine Phenytoin Carbamazepine	Ethosuximide Valproate	Valproate Lamotrigine Topiramate	Valproate Lamotrigine Topiramate
Second-line drugs	Primidone Phenobarbital Felbamate	Topiramate Primidone Phenobarbital Felbamate	Topiramate Lamotrigine Clonazepam	Primidone Phenobarbital Clonazepam Ehtosuximide Felbamate	Phenytoin Phenobarbital Primidone Clonazepam Felbamate
Add-on drugs♣	Topiramate Levetiracetam Zonisamide Gabapentin Tiagabine	? Levetiracetam ? Zonisamide	? Zonisamide	? Levetiracetam ? Zonisamide	? Levetiracetam ? Zonisamide

♣ May be effective as monotherapy but approved only as add-on agents.

Monotherapy, rather than polytherapy, is the primary treatment technique for the initial treatment of epilepsy. There are many advantages of monotherapy, including a reduced likelihood of drug-drug interactions, improved compliance, enhanced tolerability, increased ease of interpreting serum level and cost effectiveness. If the first medication is unsuccessful in achieving the goal of the best quality of life with the fewest seizures along with the fewest side effects, then an appropriate next step is to switch to another AED and use in monotherapy. It is sound to pursue monotherapy until 2 or 3 AEDs' monotherapy trials have failed. At that point, the use of polytherapy is resonable. The new AEDs may be helpful adjunctive medications for patients who respond suboptimally to conventional AEDs (Leppik, 2000).

The side effects profile (Table 7) of AEDs is important because conventional AEDs are frequently accompanied by side effects that often depended on the pharmacokinetics of the drug (Table 8), (David et al., 2002; Fourtain, 2002). Most AEDs (especially barbiturates) affect cognitive function to some degree, even in therapeutic dose. Most side effects are experienced at the initiation of therapy and can be avoided by starting with a low enough dose and increasing more slowly than recommended by the manufacturer. Table 9 provides general target doses that will usually be therapeutic.

Problematic AED interactions are common, especially among conventional AEDs. Pharmacokinetic interactions most often result from hepatic enzyme induction, which is reflected by changes in the blood level (Table 10). Overall, AED interactions are less common with the new AEDs than with the conventional AEDs because most new AEDs do not induce hepatic enzymes and are not heavily protein bounding (see Table 8). All AEDs necessarily affect the brain, so pharmacodynamic interactions make the CNS side effect of lethargy, ataxia, and blurry vision more common when more than one AED are taken at a time. Even as monotherapy, all AEDs cause CNS side effects at high doses.

Table 7. Side effects of anticonvalsant drugs (Pual, 2001).

Drug	Dose Related	Idiosyncratic
Phenytoin	Diplopia Ataxia Gingival Hyperplasia Hirsutism Coarse facial Features Ployneuropathy Osteomalacia Megaloblastic amemia	Skin rash Fever Lymphoid Hyperplasia Hepatic sysfunction Blood dyscrasia Stevens-Johnson syndrome
Carbamazepin e	Diplopia Ataxia Gastrointestinal Disturbance Diplopia Ataxia	Skin rash Blood dyscrasia Hepatic dysfunction Stevens-Johnson syndrome
Oxcarbazepin e	Hyponatremia	Skin rash
Phenobarbital	Sedation Insomnia Behavioral Dustyrbabce Duokioua Ataxia	Skin rash Stevens-Johnson
Valproic acid	Gastrointestinal Distress Tremor Sedation Weight gain Hair loss Thrombocytopenia	Hepatic dysfunction Peripheral edema
Ethosuximide	Gastrointestinal Distress Sedation Ataxia Headache	Skin rash Blood dyscrasia
Clonazepam	Sedation Diplopia Ataxia Behavioral Disturbance Hypersalivation	
Gabapentin	Drowsiness Fatigue	Drugged sensation Loss of libido
Lamotrigine	Dizziness Ataxia	Skin rash in 1-2% (frequency increased by concomitant valproic acid therapy and reduced by gradual build-up of dose) Steven-Johnson Syndrome
Vigabatrin	Sedation Vertigo Psychosis	Peripheral visual Constriction (irreversible)
Topiramate	Ataxia Confusin	Renal stones Glaucoma
Tiagabine	Dizziness Sedation Nausea	Rash
Zonisamide	Drowiness Nephrolithiasis	Ataxia Anorexia Headache Skin rash

Table 8. Pharmacokinetics of conventional and new antiepileptic drugs (Fourtain, 2002).

Drug	Metabolized by Inducible Enzymes (Mechanism)	Induces Hepatic Enzymes	Half-Life(h)	Protein Bound(%)
Cabamazepine	Yes (oxidized)	Yes	12-17	76
Ethosuximide	Yes (oxidized)	No	30-60(30 in child)	0
Felbamate	Yes (multiple mechanisms)	No	20-23	25
Gabapentin	No	No	5-7	<3
Lamotrigine	Yes (glucuronidated)	No	25 alone or w/both 60 w/ valproate 12 w/EI	55
Levetiracetam	No	No	6-8	<10
Oxcarbazepine	Yes(converted to MHD glucuronidated)	Mixed	9-11	67
Phenobarbital	Yes(hydroxylated, glucuronidated)	Yes	80-100	45
Phenytoin	Yes(hydroxylated, glucuronidated)	Yes	22	90
Primidone	Yes(similar to phenobarbital)	Yes	8-15 (shorter w/EI)	20
Tiagabine	Yes (glucuronidation, oxidation)	No	7-9(alone) 4-7(w/EI)	96
Topiramate	Yes(hydroxylated, hydrolyzed, glucuronidated)	No	20-24	13-17
Valproic acid	Yes (glucuronidate, oxidized)	No	9-16(shorter w/EI)	70-90 (varies with level)
Zonisamide	Yes/no	No	63	40

Abbreviations: EI= enzyme inducer; MHD = monohydroxy derivative.

Table 9. Titration Guidelines for Conventional and New Antiepileptic Drugs (Fourtain, 2002).

	Adult				Child	
AEDs	Dosing Schedule	Initial dose (mg)	Increment (mg)	Maintenance (mg/d)	Initial dose (mg/kg/d)	Maintenance (mg/kg/d)
CBZ	tid-qid bid <6yr.(extended release)	200 bid	200 qwk	600-1800	10	10-35 (for
ESM	qd-bid	250 qd	250 q3-7d	750	15	15-40
FBM	tid	600-1200 qd	600-1200 q 1-2wk	2400-3600	15	15-45
GBP	tid	300 qd	300 q3-7d	1200-3600	10	25-50
LTG	bid	25 qd	25 q2wk	100 w/VPA 400 alone 600 w/EI	0.15-0.5	0.5-5 w/ VPA 5 alone 5-15 w/ EI
LEV	bid	500 qd	500 qwk	2000-4000	20	40-60
OXC	bid	300 qd	300 qwk	900-2400	8-10	30-46
PB	qd-bid	30-60 qd	30 q1-2wk	60-120	3	3-6
PHT	qd (capsule) bid-tid Liquid, infatab)	200 qd	100 qwk	200-300	4	4-8
Primidone	tid	125-250 qd	250 q1-2wk	500-750	10	10-25
TGB	bid-qid	4 qd	4-8 qwk	16-32	0.1	0.4 w/o EI 0.7 w/o EI

continued

Table 9. Titration Guidelines for Conventional and New Antiepileptic Drugs (fourtain, 2002) (continued).

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	Adult				Child	
AEDs	Dosing Schedule	Initial dose (mg)	Increment (mg)	Maintenance (mg/d)	Initial dose (mg/kg/d)	Maintenance (mg/kg/d)
TPM	bid	25 qd	25 q1-2 wk	200-400	3	3-9
VPA	tid-qid (depakene, depakote)	250 qd	250 q3-7d	750-3000	15	15-45
	bid (depakote ER)					
ZNS	bid	100 qd	100 q2wk	200-400	4	4-12

Abbreviations: EI= enzyme inducer; ER= extended release; CBZ=cabamazepine; ESM= ethosuximide; FBM=felbamate; GBP=gabapentin; LTG=lamotrigine; OXC=oxcarbazepine;PB=phenobarb; PHT=phenytoin; TGB=tiagabine; TPM=topamax; VPA=valproic acid; ZNS=zonisamide; LEV=levetiracetam

Table 10. Anti-epileptic Drug Interactions Influencing Serum Concentrations*ψ(Pual, 2001).

Drug	Serum Level Influenced												
Added	CBZ	ESM	FBM	GBP	LTG	LEV	OXC	PB	PHT	TGB	TPM	VPA	ZNS
CBZ	↓	↓	↓	–	↓↓	–	↓	–	↓↑	↓↓	↓↓	↓	↓
ESM	?–	– –	?–	?–	–	?–	?–	?–	?↑	?–	?–	?–	?–
FBM	↓	?–	– –	?–	–	?–	?–	↑	↑↑	?–	?–	↑↑	?–
	Epox.↑												
GBP	–	?–	?–	– –	?–	–	?–	–	–	?–	?–	–	?–
LTG	–	–	–	?–	– –	–	?–	–	–	?–	?–	↓	?–
LEV	–	?–	?–	–	–	– –	?–	–	–	?–	?–	–	?–
OXC	–	?	?–	?–	↓	?–	– –	–	–	?	?–	–	?–
PB	↓	↓	↓	–	↓↓	–	↓	– –	–	↓↓	↓	↓	↓
PHT	↓	↓	↓	–	↓↓	–	↓	–	– –	↓↓	↓↓	↓	↓
TGB	–	?–	?–	?–	?–	?–	?–	?–	–	– –	?–	↓	?–
TPM	–	?–	?–	?–	?–	?–	?–	–	↑	?–	– –	↓	?–
VPA	↓	↓↑	–	–	↑↑	?↑	–	↑↑	–	–	↓	– –	–
	epox.↑												
ZNS	?–	–	?–	?–	?–	?–	?–	–	–	?–	?–	–	– –

Effect of adding the drug listed in the first column on the blood concentration of the drugs listed in other columns.

ψclinicaliy significant effects are double arrows; other effects (single arrows) are not usually clinically relevant. Question marks indicate unknown interactions.

Abbreviations: CBZ=cabamazepine; ESM= ethosuximide; FBM=felbamate; GBP=gabapentin; LTG=lamotrigine; LEV=levetiracetam; OXC=oxcarbazepine;PB=phenobarb; PHT=phenytoin; TGB=tiagabine; TPM=topamax; VPA=valproic acid; ZNS=zonisamide.

Mechanism-specific pathways for anti-epileptic drugs

During the past decade, knowledge of the mechanisms of seizures has greatly expanded. Distinct events occur during a seizure: initiation of the seizure, spread of the ictal activity, and arrest of the seizure (McNamara, 1994). Several fundamental mechanisms play important roles. Sodium conductances are important in the initiation and maintenance of ictal activity, calcium conductances initiate and maintain seizure activity, and also contribute to neuronal injury, and potassium conductances are essential in the arrest of a seizure discharge. The principle neurotransmitters involved in seizures are γ-aminobutyric acid (GABA) and the excitatory amino acid glutamate (Ferrendelli, 1996).

Although current knowledge is limited, the available drugs appear to use one or more of the mechanism as described below. Sodium conductances are modified by CBZ, lamotrigine (LTG), OXC, PHT, primidone, VPA, and zonisamide (ZNM). These drugs bind to the inactivated sodium channel and block rapid repetitive neuronal discharges by delaying the reactivation of this channel. Some, such as CBZ and PHT, have this as their principal mechanism, whereas others, such as VPA and LTG, have other actions as well.

Modulation of GABA-mediated chloride conductance is believed to underline the activity of many drugs. Some drugs, such as vigabatrin(VGB) and tiagabine(TGB), elevate extracellular GABA levels directly. Gabapentin(GBP) may elevate intracellular GABA levels, although this needs further study. Benzodiazepine(BZP) appear to increase the frequency of opening of the chloride channel, and barbiturates prolong GABA-mediated chloride channel opening.

Modification of calcium conductance by influencing T-calcium channels in the thalamic neurons appears to be responsible for most of the action of ethosuximide(ESM) and some of the effect of VPA. Drugs such as felbamate(FBM) and topiramate(TPM)

appear to effect the NMDA receptors to some degree. In additional, new drugs that have additional means by which physiological processes are modified are being developed (Leppik, 2000).

Drugs acting against Na^+ channels provide the treatment of choice for generalized and partial tonic-clonic seizures; those acting at the T calcium channels level afford satisfactory therapy for generalized absences, and those acting at GABA receptors are useful to treat myoclonic seizures.

The control of neurotransmitters, their receptors an ion influx is a new therapeutic approache in anti-epileptic drug therapy:

- In generalized absences, pharmacological approaches attempt to achieve: (1) NMDA receptor inactivation; (2) GABA B receptor inactivation; and (3) inactivation of low threshold T calcium currents.
- In focal epilepsy, with or without secondary generalization, and in primary generalized epilepsy, the pharmacological approaches attempt to achieve: (1) blockade of Na^+ conductance that promotes repettitive voltage-dependent discharges; (2) blockade of voltage-dependent Ca^{2+} currents; (3) inactivation of NMDA receptors and other types of the GluR superfamily; (4) an increase in K^+ conductance; (5) an increase in Cl- entry; (6) activation of GABAergic receptors; (7) interactions with cyclic nucleotide and PI systems (second messengers); and (8) Na^+, K^+-ATPase stimulation (Ure and Perassolo, 2000).

Oxcarbazepine (Trileptal®)

OXC is a new AED that has been registered as an AED in more than 50 countries worldwide since 1990 and received approval in the United States in 2000 for the treatment of partial seizures with or without secondarily generalized seizures as both adjunctive therapy and monotherapy in adults, and as adjunctive therapy for partial-onset seizures in children aged 4-16 years (Beydoun and Kutluary , 2002).

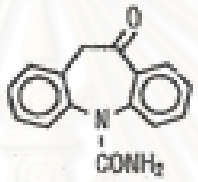

Figure 1. Structural formula of oxcarbazepine

OXC is a keto analog of CBZ chemically known as 10,11 – dihydro – 10 oxo – 5H – dibenz [b,f] azepine – 5 carboxamide (Figure 1). It is a neutral lipophilic compound with a molecular weight of 252.27 daltons and very low solubility in water (Glauser, 2001). Although structurally related to CBZ, OXC offers a number of clinically important pharmacokinetic advantages. One is its route of biotransformation. Unlike CBZ, which is metabolized by cytochrome P450 oxidative processes, OXC undergoes primarily reductive biotransformation by cytosolic enzymes, a ketone reductase to the 10 – monohydroxy metabolite (MHD), the major component of OXC (Ramsay and Wilder, 2002). Although pharmacologically active, OXC has a short half-life of only 1-2.5 hours versus a half-life of 8-10 hours for MHD, which is mainly responsible for most of its anticonvulsant effect (Beydoun, 2000).

The lack of oxidative metabolism results in two attractive properties. First, the 10,11 epoxide that contributes to adverse event profile of CBZ is not produced. In

addition, the induction and inhibition of ketone reductase is only rarely reported in the literature, so OXC has a lower propensity to inhibit or induce hepatic oxidative enzymes and therefore a diminished potential for drug –drug interactions. Also, whereas CBZ induces its own metabolism and undergoes autoinduction, the elimination of oxcarbazepine and its metabolites does not change significantly over time (Ramsay and Wilder, 2002).

Mechanisms of action

OXC and its active MHD metabolite must have multiple mechanisms of action, to account for the efficacy of OXC in epilepsy. First*, in vitro* studies have shown that one of the mechanisms of action of OXC is similar to that of CBZ and consists of the inhibition of sustained, high frequency, repetitive firing of voltage sensitive sodium channels. Second, unlike CBZ which modulates L-type calcium channels, OXC has been shown to inhibit the high–voltage active N-type calcium channels. Third, MHD reduces the frequency of penicillin-induce epileptiform spike discharge in the *in vitro* hippocampal sclice model as recorded extracellularly over the CA3 area. This effect is reversed by the potassium channel blocker 4-aminoporidine, suggesting an effect of MHD on potassium channels. Fourth, MHD appears to reduce glutamatergic transmission at corticostriatal synapses in rat slices, though the relevance of this finding to an anticonvulsant action has been questioned. Finally, OXC like CBZ, enhances dopaminergic neurotransmission. OXC and MHD have no effect at GABA or other neurotransmitter receptor binding sites (Beydoun and Kutluay, 2000; Schachter, 2002).

Pharmacokinetic properties

Although OXC is a keto analogue of CBZ and is structurally very similar (Figure 2), this slight modification in molecular structure results in major differences in biotransformation and pharmacokinetics. Unlike CBZ, the metabolism of OXC and MHD is not dependent on the cytochrome P450 hepatic enzymes, but depends largely on a ketone reductase and a uridinediphospho (UDP)-glucuronyl transferase (Ramsay and Wilder, 2002).

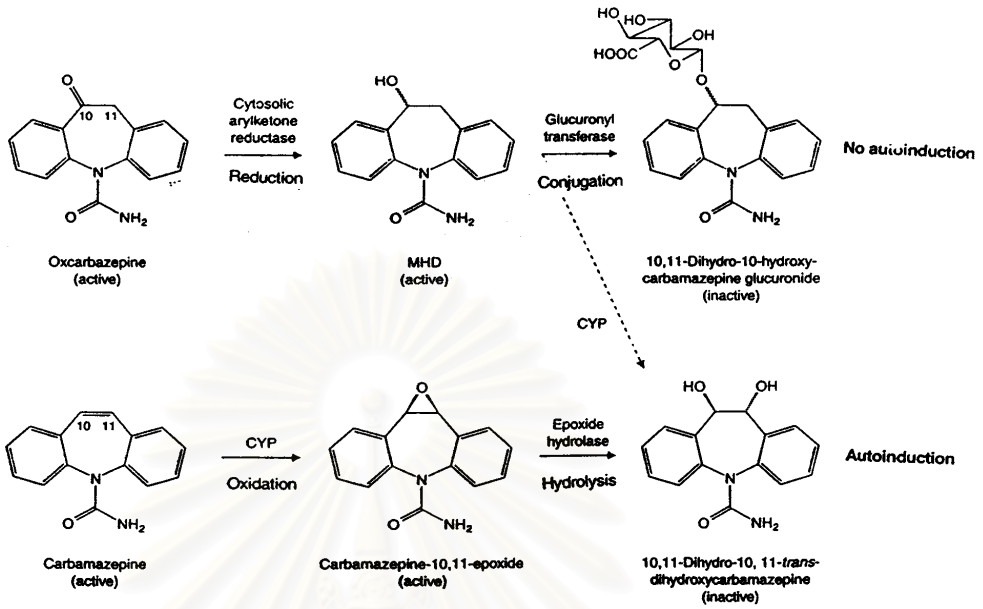

Figure 2. Molecular structures and metabolic pathways of OXC and CBZ (Beydoun and Kutluay, 2002). CBZ; carbamazepine; MHD: monohydroxy derivative; OXC: oxcarbazepine.

Once absorbed from the gastrointestinal tract, OXC is almost immediately reduced by hepatic cytosolic arylketone reductase, that are considered practically noninducible enzymes, to form the major active metabolite MHD, but a small proportion (4%) is oxidized to a pharmacologically inactive dihydroxy derivative. Subsequently, MHD undergoes glucuronidation by UDP-glucoronyl transferase (Figure 2), (Glauser, 2001). After oral administration, OXC demonstrates rapid and almost complete absorption (>95%). Its absorption exhibits linear properties. In addition, it is rapidly distributed to the body and central nervous system (Ramsay and Wilder, 2002). Maximum plasma concentrations (C_{max}) of OXC and MHD reached in 2 and 4-6 hr, respectively. The area under the plasma concentration-time curve ranges from 80 to 220 mg/L●hr. The half-life of OXC and MHD are respectively, approximately 2 and 9 h. Steady-state levels of MHD are reaches within 2-3 days of twice-daily dosing. Both the

parent compound and its metabolite exhibit linear pharmacokinetics behavior with dose proportionality observed over the dose range 300-2,700 mg. (Cloyd and Remmel, 2000).

Only 40% of MHD is bound to protein, mainly albumin, therefore interactions at the plasma protein binding sites are less likely to occur. The percentage of MHD that bound to protein is independent of its serum concentration. No autoinduction or accumulation occurred with OXC therapy in healthy volunteers. The volume of distribution of MHD ranged from 0.7-0.8 L/kg, consistent with distribution into body water. OXC is mainly eliminated by direct renal excretion (approximately 96%) as the inactive glucuronide conjugates of MHD (49%) and OXC (9%) and unchanged MHD(27%). The rate of renal clearance of MHD is 0.71 to 1.26 L/hr (Wellington and Goa, 2001). Mild to moderate renal impairment in adults has little effect on plasma MHD concentrations. However, the patients with renal failure (creatinine clearance <30ml/min/1.73 m^2), the elimination half-life of MHD is prolonged, the area under the curve (AUC) is increased 2-fold, and significant increase in plasma MHD concentrations can occur unless the dosage is adjusted. Mild to moderate hepatic impairment does not appear to affect MHD pharmacokinetics.

Mean dose-normallized, steady-state plasma MHD concentrations in children and adolescents (aged 6-18 years) adjusted for body weight were comparable to those in adults. However, the dose-normalized AUC values of MHD in children aged 2-5 years were 30% lower than those in children aged 6-12 years. Thus higher doses of OXC may be required in children younger 6 years. In contrast, peak plasma MHD levels and AUC values of MHD were significantly higher in elderly patients (aged 60-82 years) than in younger adults, which was thought to be due to age-related decreases in creatinine clearance (Glauser, 2001).

When crossing the placenta, OXC is metabolised to MHD. Maternal and neonatal plasma levels of the two compounds at delivery were in the same range (Rabasseda, 2001). The concentration of MHD in maternal milk is 50% of the serum concentration, consistent with the unbound MHD fraction (Beydoun and Kutluay, 2002).

Drug-Drug Interactions

Interactions between OXC and AEDs

Although the early studies using OXC doses of up to 600 mg/day failed to demonstrate any hepatic enzyme inducing effect, it was shown that OXC does interact with the hepatic mono-oxygenase enzymes when used at higher dosages. OXC and MHD are weak inhibitors of CYP2C19 and weak inducer of CYP 3A4/5. The inhibition of CYP2C19 isoform by high dose OXC (>1200 mg/d) can result in an increase of PHT (up to 40%) and PB (about 15%) serum levels. CBZ reduced the median AUC of MHD by 15 to 35% in clinical study, and serum CBZ concentrations were decreased (by approximately 15%) by OXC, although not to a clinically significant level. OXC had a significant inducing effect on LTG, although this was smaller than that of CBZ. The Cmax of LTG was reduced by 29% with OXC. In patients, VPA concentrations decrease an average of 18% in the presence of OXC (Cloyd and Remmel, 2000). Removal of OXC therapy in patients coadministered VPA and LTG would cause a 50% increase in serum LTG concentrations. The metabolism of OXC is enhanced by 30-40% in the presence of hepatic enzyme inducers, such as CBZ, PHT or PB (Rabasseda, 2001).

Interactions between OXC and other drugs

OXC induces specific isoenzymes of the CYP3A group (CYP3A4 and CYP3A5) which are involved in the metabolism of dihydropyridine calcium antagonists, oral contraceptives containing ethinyloestradiol and levonorgestrel, lidocain, verapamil, diltiazem and quinidine. So, concomitant administration should be aware. It is therefore important that women on OXC take higher doses of oral contraceptives or use an additional contraceptive method in order to prevent unwanted pregnancies. There are no clinically relevant drug-drug interactions between OXC and dextropropoxyphene, erythromycin or cimetidine. Verapamil causes a 20% decrease in MHD plasma levels. In addition OXC can be safely administered to patients on warfarin therapy (Glauser, 2001).

Side effects

OXC is reported to be safer and better tolerated than CBZ and other classic AEDs. The most common side effects include headache, somnolence/fatigue, dizziness, viral infection and nausea. Other less common side effects associated with the central nervous system include psychomotor slowing, difficulty with concentration, speech/language problems and coordination abnormalities. OXC is also less sedative than CBZ and has a lower potential for hypersensitivity (Rabasseda, 2001). A rash was reported in about 4-5% of patients exposed to OXC, with disappearance of the rash in all patients following the discontinuation of the drug. As with CBZ, treatment with OXC can result in hyponatremia. Sodium level <125 mEq/L were reported in 2.5% of patients receiving OXC therapy. However, it increased after discontinuation of OXC. The risk of OXC-induced hyponatremia is age-dependent, (Beydoun and Kutluay, 2002). Patients who have had a hypersensitivity reaction to carbamazepine should be informed that 25-30% of them would experience hypersensitivity to OXC (Beydoun, 2000).

Clinical efficacy

The efficacy and tolerability of OXC were assessed in 10 large, controlled trials (Table 8), (Glauser, 2001). All were randomized, double-blind, controlled parallel-design studies involving patient with partial-onset seizures with or without secondarily generalized seizures.

Table 11. Major controlled trials assessing OXC efficacy, safety, and tolerability in patients with partial-onset seizures (Glauser, 2001).

Study Design	Dosage Regimen	Nature of Seizure	Age range (years)	No. of Patients
Monotherapy Placebo-controlled	OXC 1200 mg/d vs placebo	recent onset	8-69	67
Monotherapy Placebo-controlled	OXC 2400 mg/d vs placebo	refractory	11-62	102
Monotherapy Substitution dose-controlled	OXC 2400 vs 300mg/d	refractory	12-65	143
Monotherapy Substitution dose-controlled	OXC 2400 vs 300mg/d	refractory	11-66	87
Monotherapy Substitution dose-controlled	OXC 2400 vs 300mg/d	refractory	12-65	143
Monotherapy Substitution dose-controlled	OXC 2400 vs 300mg/d	refractory	11-66	87
Monotherapy Comparative	OXC 2400 vs VPA 2400mg/d (max. dosages)	recent onset	15-65	249
Monotherapy Comparative	OXC 2400 vs PHT 800mg/d (max. dosages)	recent onset	15-91	287
Monotherapy Comparative	OXC 2400 vs PHT 800mg/d (max. dosages)	recent onset	5-17	193
Monotherapy Comparative	OXC 1800 vs CBZ 1400mg/d (max. dosages)	recent onset	14-63	235
Adjunctive Placebo-controlled	OXC 600, 1200, 2400mg/d vs	refractory	15-65	692
Adjunctive	OXC 30-46mg/kg/d vs	refractory	2-17	267

continued

Table 11. Major controlled trials assessing OXC efficacy, safety, and tolerability in patients with partial-onset seizures (continued).

Efficacy	Tolerability	Primary efficacy (E) and Tolerability (T) Variable
OXC>placebo (p=0.0457)	NA	(E) Time to first seizure
OXC>placebo	NA	(E) Time to meeting one of the exit criteria (p=0.0001)
OXC2400mg/d> 300mg/d (p=0.0001)	NA	(E) Time to meeting one of the exit criteria
OXC2400mg/d> 300mg/d (p<0.0001)	NA	(E) % of patients meeting one of the exit criteria
OXC=VPA	OXC=VPA	(E) % Of seizure-free patients during maintenance therapy (T) Time to premature discontinuation of drug due to adverse experience
OXC=PHT	OXC>PHT (p=0.02)	(E) % Of seizure-free patients during maintenance therapy (T) Time to premature discontinuation of drug due to adverse experience
OXC=PHT	OXC>PHT (p=0.02)	(E) % Of seizure-free patients during maintenance therapy (T) Time to premature discontinuation of drug due to adverse experience
OXC=CBZ	OXC=CBZ(T1) OXC>CBZ(T2)	(E) % Of seizure-free patients during maintenance therapy (T1) % Of patients with adverse experience (T2)% Of patients with severe adverse experience requiring withdrawal from trial
OXC>placebo (p=0.0001)	NA	(E) %change in partial seizure frequency/28day
OXC>placebo (p=0.0001)	NA	(E) %change in partial seizure frequency/28day

NA = not applicable, since no tolerability primary outcome variable was identified for statistical analysis. In this study, only descriptive adverse event data were presented.

In the monotherapy trials, patients had either partial seizures or generalized tonic-clonic seizures without partial onset. Four basic study designs were used: monotherapy placebo-controlled (i.e., monotherapy OXC vs monotherapy placebo, two studies), monotherapy substitution dose-controlled (i.e., high-dose OXC vs low-dose

OXC, two studies), monotherapy comparative (i.e., OXC vs standard AED, four studies), and adjunctive placebo-controlled (i.e., OXC adjunctive therapy vs placebo adjunctive therapy, two studies). The studies show that OXC monotherapy at a daily dose of 15-20 mg/kg (approximately 900-1200 mg in adults) achieves complete seizure control in about 60% of previously untreated adults, adolescents, and children with partial epilepsy. OXC has similar efficacy compared with current standard AEDs (CBZ, PHT, VPA) in patients newly diagnosed partial epilepsy (Schmidt and Sachdeo, 2000).

The two adjunctive therapy mentioned above was studied in multi-center, placebo controlled, parallel-group randomized control trials for adults (Barcs et al., 2000) and children (Glauser et al., 2000) with medically refractory partial epilepsy. The first was a multicenter, randomized, four-arm, parallel-group trial with OXC at daily doses of 600,1200, and 2400 mg in patients aged 15-65 years, with medically refractory partial epilepsy, maintained on one to three AEDs. The efficacy was determined by comparing the percentage change in seizure frequency during double-blind treatment compared with baseline for the OXC and placebo groups. The results of efficacy analysis demonstrated a dose-response relationship, with a median reduction in seizure frequency for placebo, OXC 600, 1200, and 2400 mg/d of 8%, 26%, 40%, 50%, respectively. All OXC-treated patients showed significant improvement compared with placebo-treated patients ($p=0.0001$). The response rate (i.e., percentage of patients with $\geq$ 50% reduction in seizure frequency/28 days relative to the baseline phase) in the 600, 1200, and 2400 mg/d groups was 27%, 41%, 50%, respectively, compared with 13% in placebo group (each $p \leq 0.0008$).

The most common adverse events (AEs) were related to the central nervous system (dizziness, headache, somnolence, ataxia, nystagmus, abnormal gait) and digestive system (vomiting, nausea, abdominal pain). Some AEs appeared to be dose related: dizziness, diplopia, somnolence, vomiting, nausea, ataxia, nystagmus, abnormal vision, vertigo and abnormal gait. Overall, no clinically noteworthy trends were observed in vital signs or laboratory values. The results support the efficacy of adjunctive therapy in patients with refractory partial seizures, which include the seizure subtypes of simple, complex, and partial seizures evolving to secondary generalized tonic-clonic seizures.

The second adjunctive therapy trial evaluated the effectiveness of OXC in children aged 3-17 years, with inadequately controlled partial seizures, maintained on one or two AEDs. A flexible titration schedule was used; dosage could be adjusted to tolerated dosage. The target randomized dosage for the appropriate weight category (30-46 mg/kg/d) was not exceeded. Efficacy variables were the same in both trials. As demonstrated with adults, OXC was found to be an effective adjunctive therapy in children. The median partial-seizure frequency decreased from baseline by 35% in patients treated with OXC compared with a median reduction of 9% in patients receiving placebo (p=0.0001). Premature discontinuations due to AEs were 10%(14/138) in the OXC group and 3% (4/129) in the placebo group. The most common AEs resulting in premature discontinuation were vomiting and nausea. Overall, no clinically noteworthy trends were observed in vital signs or laboratory values. Finally, the results showed that OXC adjunctive therapy is safe, effective, well tolerated and dose-response related (Beydoun, 2000; Mattson, 2002).

OXC can be initiated at a clinically effective dosage of 300 mg twice/day. However, clinical experience suggests that a starting dosage of 150 mg twice/day is much better tolerated. The dosage can be stepwise increased in 300-600 mg increments. Typically, the effective daily dose range for patients with newly diagnosed epilepsy is 600-1200 mg; for patients with medically refractory partial epilepsy, daily doses up to 2400 mg may be needed. Dosage adjustment of OXC is recommended for patients with creatinine clearance below 30 ml/min (Beydoun, 2000).

In Thailand, OXC was registered as a new AEDs under the name “ Trileptal®” in 2001. By the Safety Monitoring Program scheme, OXC will be exclusively available in hospitals until the status of new drug is removed by evidence proving of its efficacy and safety in Thai patients. Until now there is no appreciable information on such data, therefore we consider it interesting to evaluate the efficacy and safety of OXC as an add-on therapy in Thai patients with refractory partial seizure using a randomized, double-blind and dose controlled design comparing between OXC at 600 and 1200 mg/d.

CHAPTER III

MATERIALS AND METHODS

In the present study, clinical study was conducted in epileptic outpatients at Epilepsy Clinic of Pramongkutklao Hospital, Bangkok, Thailand during April 2003 to January 2004. Determination of plasma concentration of MHD was carried out at the Department of Pharmacology, Faculty of Pharmaceutical Sciences, Chulalongkorn University.

The study protocol was approved by the Ethical committee Of Pramongkutklao Hospital and Faculty of Pharmaceutical Sciences, Chulalongkorn University. All patients were given information of the study protocol and provided written informed consent before entering the trial.

Materials

Instruments

Automatic pipet (Pipetman Gilson®, France)

High Performance Liquid Chromatography (Shimadzu®, Japan)

Vacuum pump (GE®motors, U.S.A.)

Refrigerated centrifuge (ALC® 4277 R, Japan)

Vortex mixture (Clay® adam, U.S.A.)

Sonicator (Elma®, Germany)

Digital balance (Mettler® AJ 180, Switzerland)

Hot air oven (Memmert®, Germany)

Chemicals

10,11-dihydro-10- hydroxycarbamazepine (MHD), [kindly provided by Novartis, Switzerland]

Dichloromethane HPLC grade (LAB-SCAN, Thailand)

Acetronitrile HPLC grade (LAB-SCAN, Thailand)

Ethanol HPLC grade (LAB-SCAN, Thailand)

Methanol HPLC grade (LAB-SCAN, Thailand)

Nitrogen gas

Distilled water

Blank capsules [kindly provided by Capsule Products, Thailand]

Lactose [kindly provided by Department of Manufacturing Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University.]

Methods

1. Determination of plasma MHD concentration

1.1 Validation

Analytical method validation includes all of procedures recommended to demonstrate that a particular method for the quantitative measurement of MHD in plasma is reliable and reproducible (Shah et al., 1991;Causon, 1997). The parameters of the validation for this methods include selectivity, linearity, within-run and between-run precision, accuracy, and recovery.

1.1.1 Selectivity

Selectivity includes the ability to separate the analyst from degradation products, metabolites and co-administered drugs. Blank human plasma samples from six different human sources were evaluated to determine the presence of any interference across the retention windows of MHD.

1.1.2 Linearity

The linearity of an analytical methods is its ability to elicit test results that are directly, or by a well defined mathematical transformation, proportional to the concentration of analyst in samples within a given range. Linearity can be expressed as

a calibration curve which is the relationship between instrument response and known concentration of the analyst. A calibration curve should be prepared in the same biological matrix as the samples in the intended by spiking with known concentrations of the analyst.

The stock solution of MHD in 20% ethanol in water was prepared and 10 μL was added to a 90 μL aliquots of blank plasma. The standard mixture of MHD ranged 2.5-40 μg/mL. MHD standards were prepared and analyzed as described in section 1.2. Peak area and concentrations of each analyst was plotted and the relationship between these variables was assessed by regression analysis.

1.1.3 Precision

The precision of a bioanalytical method is a measure of the random error and is defined as the agreement between replicate measurements of the same sample. Precision can be considered as having a within assay batch component or repeatability which defines the ability to repeat the same methodology with the same analyst, using the same reagents in a short interval of time, e.g. within a day. This is also known as intra-assay precision. The ability to repeat the same methodology under different conditions, e.g. change of analyst, reagents or equipment; or on subsequent occasions, e.g. loss several days or weeks, is covered by the between batch precision or reproducibility, also known as inter-assay precision.

- Intra-assay

  plasma samples spiked with MHD at 7.5, 15, 30 μg/mL were prepared and analyzed as described in section 1.2.

- Inter-assay

  The inter–assay was evaluated over three days with five replicates of plasma samples being prepared in the same manner as those described in intra -assay.

The precision is expressed as the percent coefficient of variation (%CV) of the replicate measurements. The %CV value should be within 15% except at LOQ, where it should not deviate by more than 20%.

$$\%CV = (\text{standard deviation} / \text{mean}) \times 100$$

1.1.4 Accuracy

The accuracy of an analytical method is the closeness of mean test results obtained by the method to the true value of the analyst. The amount of analyst added and found in spiked plasma sample obtained from section 3.4 were used to calculate the accuracy of the developed method. Accuracy is reported in terms of percent recovery which is calculated from the expression:

$$\% \text{ Recovery} = \frac{\text{measured value concentration}}{\text{Known concentration}} \times 100$$

The accuracy of method should be within $\pm$ 15%.

1.1.5 Recovery

The recovery of an analyst in an assay is the detector response obtained from an amount of the analyst added to and extracted from plasma, compared to the detector response obtained for the known concentration of pure standard. Recovery relates to the extraction efficiency of analytical method within the limits of variability.

Set A:Five replicates blank plasma spiked with MHD at 7.5,15,30 μg/ mL were prepared and carried out the entire procedure as described in section 1.2.

Set B:Five replicates unextracted standards at concentration of 7.5,15,30 μg/mL were prepared and carried out the entired procedure as described in section 1.2.

Extraction efficiency was calculated by comparing peak area obtained from spiked MHD standard, set A with those obtained from set B. Values for absolute recovery of method not less than 90% have been used as numerical acceptance limits.

$$\text{Absolute recovery} = \frac{\text{response of analyst spiked into matrix (processed)}}{\text{response of analyst of pure standard(processed)}} \times 100$$

1.2. **Measurement of plasma MHD concentration**

- To plastic centrifuge tubes, 100 μL of plasma sample was added. For the extraction step, to each tube, 3 mL of dichloromethane was added. The tubes were mixed 10 min, then centrifuged at 4,000 rpm for 10 min. Two mL of the organic phase were removed and evaporated to dryness under nitrogen gas. The residue was dissolved in 200 μL of the mobile phase, and 30 μL was injected into the column of chromatography (Matar et al., 1995).

- Chromatographic conditions

  Column: C18 (4μm, 150 mm ×3.9 mm I.D.) with guard column

  Detector: UV wavelength 215 nm

  Flow rate: 1.5 mL/min

  Mobile phase: Water : Acetronitrile = 80 : 20

  Temperature : Room temperature

2. Study Protocol

2.1 Study population

Subjects were recruited from epileptic outpatients of Epilepsy Clinic of Pramongkutklao Hospital with the following criteria. Seizure types were classified according to the International League Against Epilepsy 1981 and 1989 Classifications.

Inclusion criteria

1. Male and female patients aged between 15 and 65 years with inadequately control partial seizures classified as simple, complex or partial seizures evolving to secondarily generalized seizures, were enrolled in the study.
2. Patients were eligible for randomization in the study if they had
   2.1 Experienced at least 4 partial seizures during the 56-day baseline period(at least average one of which occurred during each of two 28-day period of this).
   2.2 Receiving a stable regimen of one or more AEDs. (if the patients were receiving only one currently AEDs, they must have previously failed in the treatment with any available AEDs, as monotherapy or in combination.
   2.3 Dosage regimen of primary concomitant AEDs was above the average recommended effective dose or at its maximally tolerated dose, and the others had to be at least at the recommended minimum effective dose.

Exclusion criteria

1. A serum sodium concentration less than 130 mEq/L
2. A history of status epilepticus in 3 months preceeding randomization
3. Significant liver, kidney insufficiency, psychiatric illness,a progressive structural lesion in the CNS or a progressive encephalopathy
4. Use of dihydropyridine calcium channel blockers or monoamine oxidase inhibitors
5. History of OXC therapy
6. Pregnant or lactating women

Exit criteria

During the double-blind treatment phase, patients were required to exit the study if they experienced any of the following events:

1. Pregnancy
2. Whenever the patient or the physician decided that it was for the patient's best interest
3. Intolerable adverse experiences
4. Any major violation of the trial protocol

2.2 Study design

This study was a randomized, double-blind, dosage-controlled, parallel-group trial comparing the efficacy and safety of two doses of OXC (600 mg/d and 1200 mg/d) administered as adjunctive therapy. The study consisted of three phases as follows (Figure 3):

2.2.1 Baseline Phase (56 days)

2.2.2 Double - blind Treatment Phase (98 days)

Consisted of 2.2.2 a) a Titration period (14 days)

2.2.2 b) a Maintenance period (84 days)

2.2.3 Open - label Extension Phase

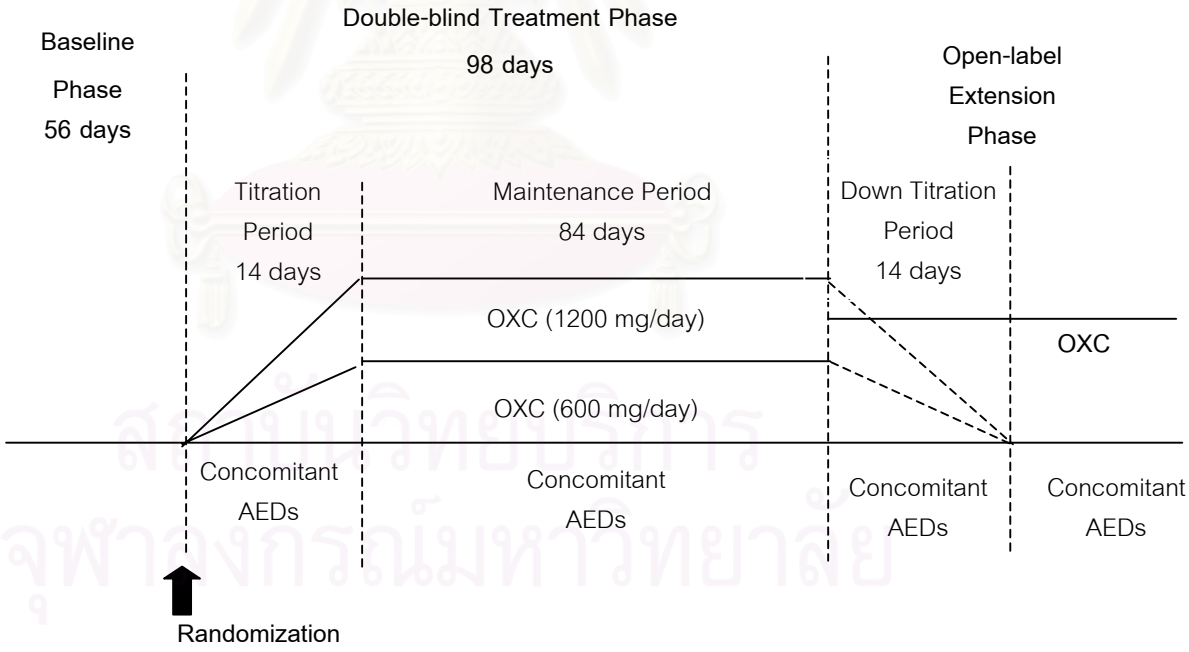

Figure 3. Trial design. AEDs = antiepileptic drugs ; OXC = oxcarbazepine.

2.2.1 Baseline Phase (56 days; 8weeks):

a) Before enrollment in to the baseline phase, potential subjects were recruited and the study plan was explained in detail. They were maintained on a stable dose of their current AED(s), and were required to keep a seizure diary throughout the duration of the trial (22 weeks) to document the dates, times, descriptions of their seizures and adverse events of the trial drug.

b) At the end of baseline period, patients who complied with inclusion criteria were asked to complete informed written consent before being assessed by the following screening procedures to achieve baseline data (visit 1) or being excluded if any of the exclusion criteria was demonstrated. The screening procedures included

- a complete physical and neurological examination
- measurement of vital sign
- determination of medical and epilepsy history
- recording of concomitant medication/therapy use
- clinical laboratory testing (routine blood chemistry analysis, hematology, and urinalysis)
- determination of plasma concomitant AED(s) concentration

c) Eligible patients were randomized to receive OXC either 600 or 1200 mg/d as home medication. Study medication was formulated as identical blinded capsules. Physician and patients were blinded to the identity of the trial drug codes.

2.2.2 Double-blind Treatment Phase (98 days; 14 weeks):

a) At the beginning of double-blind treatment phase, patients were entered into a 14-day titration period and the first dose of OXC (according to their dosage group) was added to their currently used AEDs. Target doses (600 or 1200 mg/d) were achieved through a titration schedule within 14 days as shown in Table 12. After that patients will maintain at target dosage throughout the 84-day maintenance period. In addition, dosage of concomitant AEDs were maintained as it was in baseline period, however the dosage could be decreased by physician if needed e.g. if adverse effects occurred.

Table 12. Oxcarbazepine dosing schedule

Group	Double-blind Treatment Phase(98 days)			
	Titration period (14 days)		Maintenance period (84 days)	
	Day	Dosage regimen	Day	Dose
600 mg/d	1-12	150mg bid	15-98	600mg/d(300mg bid)
	13-14	300mg bid		
1,200mg/d	1-6	300mg bid	15-98	1200mg/d(600mg bid)
	7-12	450mg bid		
	13-14	600mg bid		

b) During maintenance period, patients returned to the clinic with seizure diary for evaluations of efficacy and safety at 28-day intervals for 3 times (visit 2 - 4). In each visit, physical and neurological examinations, assessment of compliance by medication count, checked type and frequency of seizures and documented AEs, recording of concomitant medication/therapy use, performed clinical laboratory testing (routine blood chemistry analysis, hematology, urinalysis), measured plasma concomitant AEDs concentration and plasma concentration of MHD (the pharmacologically active metabolite of OXC) were measured and recorded as shown in Table13.

Table 13. Oxcarbazepine study protocol

Variable	Oxcarbazepine study protocol			
	Visit			
	1	2	3	4
Time (day)	0	43	71	99
	baseline phase	◄—— treatment phase ——►		
Consent	x			
Initial history	x			
Interval history		x	x	x
Seizure count, type	x	x	x	x
Complete physical Examination	x	x	x	x
Neurological examination	x	x	x	x
Hematology (CBC, Differential platelets)	x	x	x	x
Routine blood chemistry[a]	x	x	x	x
Urinalysis	x	x	x	x
Antiepileptic drug Levels	x	x	x	x
Pill count		x	x	x
Adverse event		x	x	x
MHD level			x	x

[a] serum glutamic oxaloacetic transaminase(SGOT), serum glutamate pyruvate transaminase(SGPT), Alkaline phosphartase(ALP), Fasting blood sugar(FBS) ,Blood urea nitrogen(BUN), Creatinine clearance(CrCl), electrolytes(K^+, Na^+)

c) To determine therapeutic plasma MHD concentration, the average MHD plasma concentrations (μg/mL) during steady state were determined using blood samples collected **before the morning dose** of visits 3 and 4 during the double-blind treatment phase. Approximately 3 mL of venous blood was obtained in Venoject (lithium heparin) tubes. Samples were centrifuged immediately at 3000 rpm for10 min, and plasma was transferred to a clean polypropylene tube and frozen immediately. The plasma samples were

frozen at – 20 °C or lower during storage until analysis. MHD Plasma concentration were determined by high-performance liquid chromatography (HPLC) (William et al., 2003).

2.2.3 Open-label Extension Phase:

a) At the end of the double-blind treatment phase, double-blind code was disclosed, the patients were given the option to enter an open-label extension phase of the study or discontinue OXC. This phase is ongoing, hence, only results from the double - blind treatment phase are reported here.

b) In case of withdrawal, OXC was gradually withdrawn from their regimens over a 14-day period.

2.3 Assessment of efficacy and safety

2.3.1. Clinical efficacy evaluation (Barcs, 2000)

Efficacy data were collected at visit 2-3 by self-reported seizure diaries in which patients or their caregivers recorded the data of each seizure. At each study visit, the number and type of seizures were recorded. The total number of seizure that occurred since the previous visit was reported as the seizure count for each seizure type.

The primary efficacy endpoint

The primary efficacy endpoint was the percentage reduction or the percent change in seizure frequency (PCH) per 28 days during double-blind treatment phase in relation to the baseline phase [seizure frequency per 28 days was defined as a total seizure(all types) count from the specified trial period devided by the number of days with valid seizure counts recorded in patient diaries, multiplied by 28(days)].

PCH is calculated as the difference between seizure frequency during treatment (T) and baseline (B), expressed as a percentage of baseline frequency: PCH = 100 (T-B) / B

The secondary efficacy end point

The secondary efficacy end point was treatment response or responder rate. Responder rate is the percentage of patients with a 50% or greater reduction in seizure frequency during the double-blind treatment compared to baseline phase.

2.3.2. Safety evaluation

The safety of OXC was evaluated by comparing baseline physical/neurological examinations, vital signs, and laboratory data with data collected during the treatment. In addition, adverse events (AEs) were monitored throughout the trial.

2.4 Data analysis and statistical methods

2.4.1 Sample size

A sample size of 30 patients (15 patients per treatment group) was chosen to provide 80% power to detect a 45% difference in percentage change from baseline in partial seizure frequency per 28 days between the group of OXC 600 mg/d and 1200 mg/d, for a two side test with α = 0.05.

2.4.2 Efficacy

a) The primary efficacy endpoint (PCH) were analyzed by using

1. A Wilcoxon Signed Ranks Test to compare during before (baseline phase) and after (double-blind treatment phase) treatment.
2. A Regression Analysis with dose, sex, age, weight, baseline seizure frequency and plasma MHD concentration as contribuable variable.
3. A Wilcoxon Rank-Sum Test as previously reported (Barcs et al, 2000) to compare efficacy between 2 treatment groups.

Assuming the null hypothesis and the alternative hypothesis are

Ho : OXC at dosage 1200 mg/d have the same or less efficacy than OXC 600 mg/d.

H1 : OXC at dosage 1200 mg/d have more efficacy than OXC 600 mg/d.

b) The secondary efficacy end point (Response to treatment) was analyzed by comparing percentage of patients who experienced $\geq$50% reduction in seizure frequency between 2 treatment groups.

c) The plasma MHD concentrations and dosage regimen relationship were assessed using an average minimum plasma concentration (concentration before the morning dose) of MHD during steady state from visit 3,4 as an contribuable variable for the dosage.

2.4.3 Safety

Safety variables were summarized by treatment group, with incidence of AEs (%AEs).

CHAPTER IV

RESULTS

1. Validation of analytical method for the determination of MHD by HPLC

1.1 Selectivity

A representative of blank plasma in Figure 4 was compared with MHD plasma in Figure 5. It was clear that responses of interferences in plasma sample was outside the retention time of MHD (6.324 min), indicating the selectivity of the method for the determination of MHD.

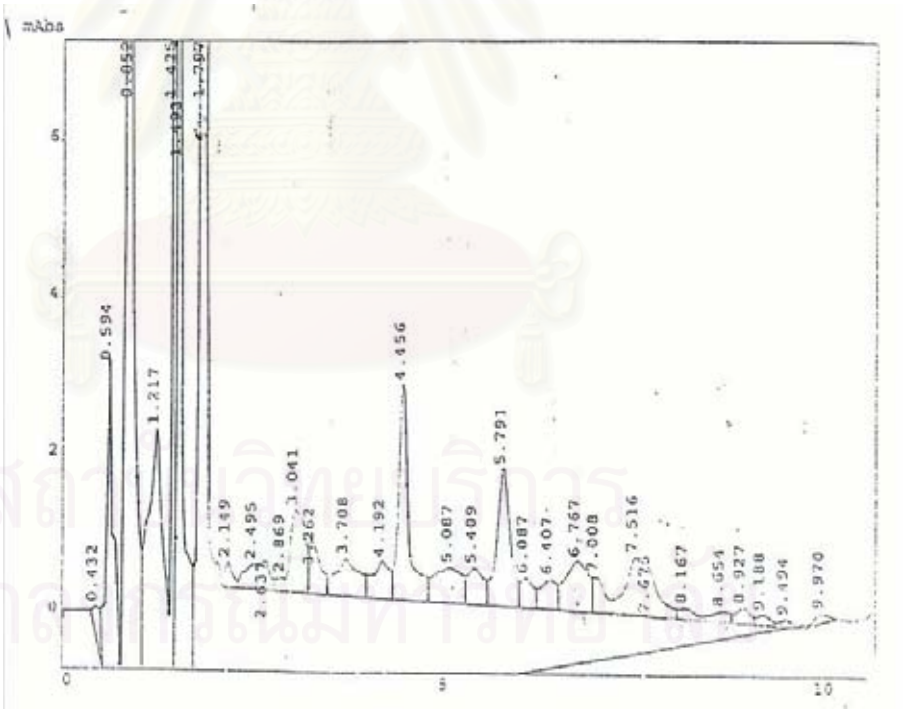

Figure. 4 Representative chromatograms of blank plasma

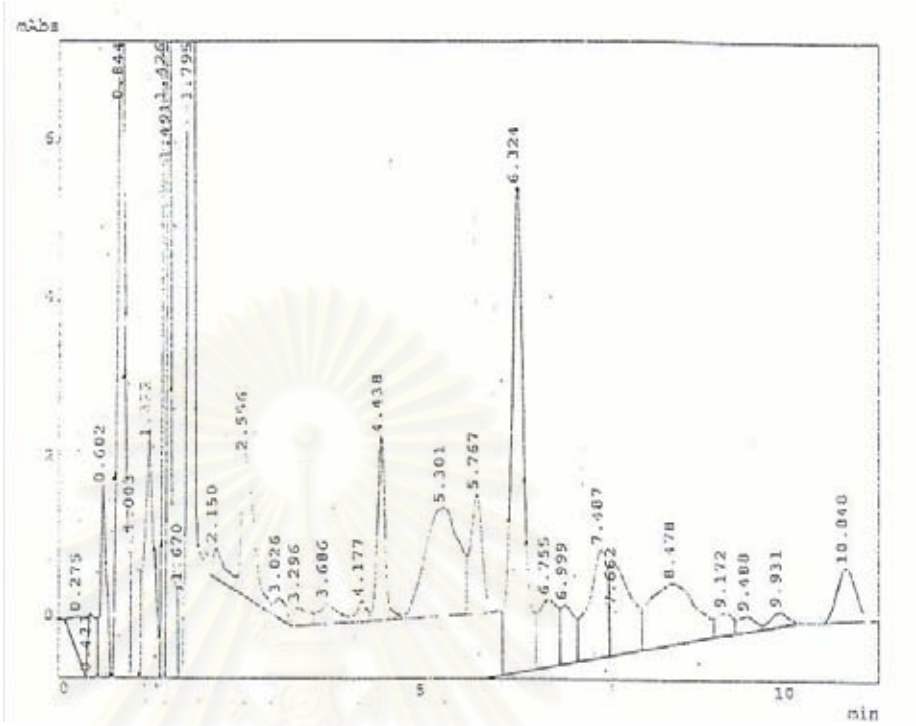

Figure. 5 Representative chromatograms of MHD added to bank plasma

1.2 Linearity

The calibration curve of the OXC in the range of 2.5-40 μg/mL was illustrated in Figure 6. This curve demonstrated a linear relationship between MHD plasma concentrations and peak area of chromatograms with the coefficient of determination (R^2) = 0.9998.

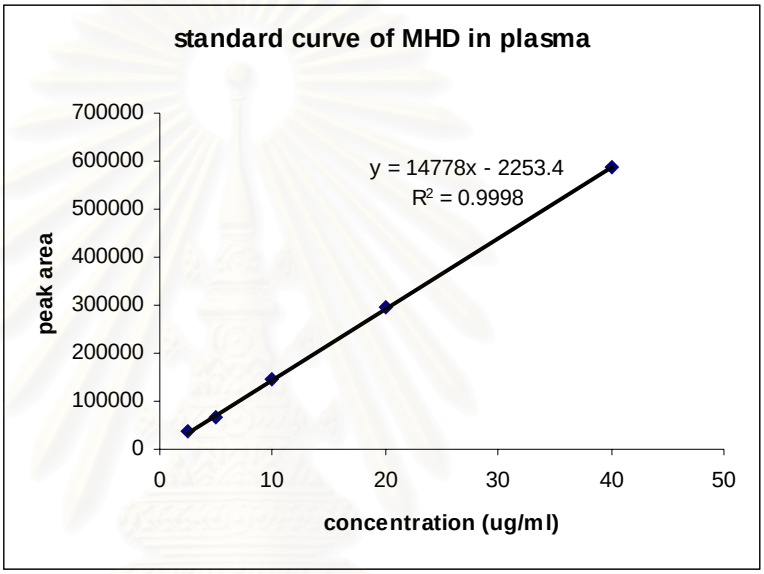

Figure. 6 Standard curve of MHD in plasma (conc. 2.5-40 μg/mL)

1.3 Precision

Five replicate of MHD plasma at 30, 15, and 7.5 μg/mL was detected by HPLC method, %CV (precision) within 15% was presented in Table 14 and 15.

Table 14. The value of precision; %CV (intra – assay)

Concentration (μg/mL)	Inversely Estimated Concentration (μg/mL)					Mean ±S.D.	%C.V.
	1	2	3	4	5		
7.5	7.29	7.04	7.52	7.57	7.22	7.33±0.22	2.99
15	14.86	14.40	14.27	14.23	14.41	14.43±0.25	1.75
30	31.74	30.92	30.62	29.75	31.74	30.95±0.84	2.71

Table 15. The value of precision; %CV (inter – assay)

Concentration (μg/mL)	Inversely Estimated Concentration* (μg/mL)					Mean ±S.D.	%C.V.
	1	2	3	4	5		
7.5	7.53	7.33	7.29	8.62	8.34	7.82±0.62	7.89
15	14.09	14.43	15.28	16.12	15.14	15.01±0.79	5.29
30	29.57	29.95	29.98	31.48	32.91	30.77±1.39	4.55

*Results are mean of five samples per concentration in each day

1.4 Accuracy

Five replicated of MHD plasma at 30, 15, and 7.5 μg/mL was measured by HPLC method, the result showed % Recovery (accuracy) within ± 15%(85-115%) of this method (Table 16).

Table. 16 The value of accuracy (%Recovery)

Concentration (μg/mL)	Peak Area*	Inversely Estimated Concentration* (μg/mL)	%Recovery*
7.5	106027.30	7.33	97.73
15	211053.30	14.43	96.20
30	440362.10	29.95	99.83

*Results are mean of five samples per concentration on the same day

1.5 Absolute Recovery

The result displayed % Absolute Recovery of this method (Table. 17), all of the results were shown nearly 100%

Table. 17 The value of % Absolute Recovery

Concentration (μg/mL)	Peak Area*		%Absolute recovery*
	Pure standard MHD	MHD spiked into plasma	
7.5	125547.00	125346.00	99.84
15	240176.00	235284.00	97.96
30	445355.00	430996.00	96.77

*Results are mean of five samples per concentration

2. Evaluation of efficacy and safety of OXC

2.1 Patient characteristics

A total of 39 patients were randomized to double-blind treatment with OXC 600 mg/d (n=20; 51%) or 1200 mg/d (n=19; 49%). Demographic and baseline seizure characteristics are summarized in Table 18. There is no difference between the two dosage groups with regard to age, sex, and weight. The patient population included 20 men (51%) and 19 women (49%); mean age was 31.6 years and mean weight was 60 kg. The types and frequencies of partial seizures in both groups during the baseline phase were similar. The median partial seizure frequency per 28 days during the baseline phase was 4.5 in the 600mg/d OXC group and 4 in the 1200mg/d OXC group. The majority of patients were receiving one concomitant AEDs (20/39; 51%), (Table 18). The most frequently prescribed concomitant AED was CBZ (22/39; 56%), followed by VPA (15/39; 39%), and PHT (14/39; 36%) (Table 19). On average, the patients were taking 1.83$\pm$0.79 concomitant AEDs in the 600 mg/d and 1.47$\pm$0.8 in the 1200 mg/d OXC group. No significant difference was observed on characteristics between two dosage groups (p=0.185).

Of the 39 patients randomized, 35 (90%) completed the double-blind treatment phase and 4(10%) discontinued treatment prematurely (2 patients in each OXC treatment group, Figure 7). Three patients (2 patients in the 600mg/d OXC group and one in 1200 mg/d OXC group) discontinued because of AEs and one patient in 1200 mg/d group was lost follow-up. Thus for the efficacy analysis, 35 of all patients were analyzed by per protocol analysis whereas safety analysis included all patients (intention-to-treat analysis).

Table 18. Baseline demographic and clinical characteristics for all randomized patients

Characteristic	OXC (mg/d) 600 n=20	1200 n=19	total n=39
Sex [no. (%)]			
Males	12(60)	8(42)	20(51)
Females	8(40)	11(58)	19(49)
Age [y]			
Mean±SD	30.4±7.3	31.7±6.9	31.6±7.1
Range	18-44	18-44	18-44
Weight [kg]			
Mean±SD	58.4±10.5	61.7±11.1	60.0±10.8
Range	42-78	46-80	42-80
28-day baseline seizure frequency[Median (mean)]			
- All partial	4.5(7.6)	4.0(7.7)	4(7.7)
- Complex partial	3.0(6.0)[n=16]	3.0(5.7)[n=17]	3(5.8)[n=33]
- Simple partial	4.5(10.5)[n=4]	7.0(7.3)[n=6]	5.0(8.6)[n=10]
- Secondarily generalized tonic-clonic	1.5(2.9))[n=5]	3.0(3.0))[n=2]	1.5(2.9)[n=7]

Table 19. Number of patients using concomitant AEDs by treatment group;n(%).

Number of AEDs	Treatment group		Total (n=39)
	OXC (mg/d)		
	600 (n=20)	1200 (n=19)	
1	7(35%)	13(68%)	20(51%)
2	8(40%)	2(11%)	10(26%)
3	5(35%)	4(25%)	9(23%)

Table 20. Distribution of concomitant AEDs use in all patients and responder ; n (%).

Concomitant AEDs	Patients using concomitant AEDs					
	OXC (mg/d)					
	600 (n=20)		1200 (n=19)		Total	
	All patients	Responder*	All patients	Responder*	All patients	Responder*
CBZ	13(65%)	5(38%)	9(47%)	4(44%)	22(56%)	9(41%)
VPA	11(55%)	4(36%)	4(21%)	2(50%)	15(39%)	6(40%)
PHT	8(40%)	3(38%)	6(32%)	3(50%)	14(36%)	6(43%)
PB	3(15%)	1(33%)	7(39%)	1(14%)	10(26%)	2(20%)
TPM	1(5%)	1(100%)	3(16%)	2(67%)	4(10%)	3(75%)
LTG	2(10%)	0(0%)	0(0%)	0(0%)	2(5%)	0(0%)

Abbreviations: CBZ=cabamazepine; LTG=lamotrigine; PB=phenobarb; PHT=phenytoin; TPM=topamax; VPA=valproic acid.

* Responder= patients who had ≥50% reduction in seizure frequency

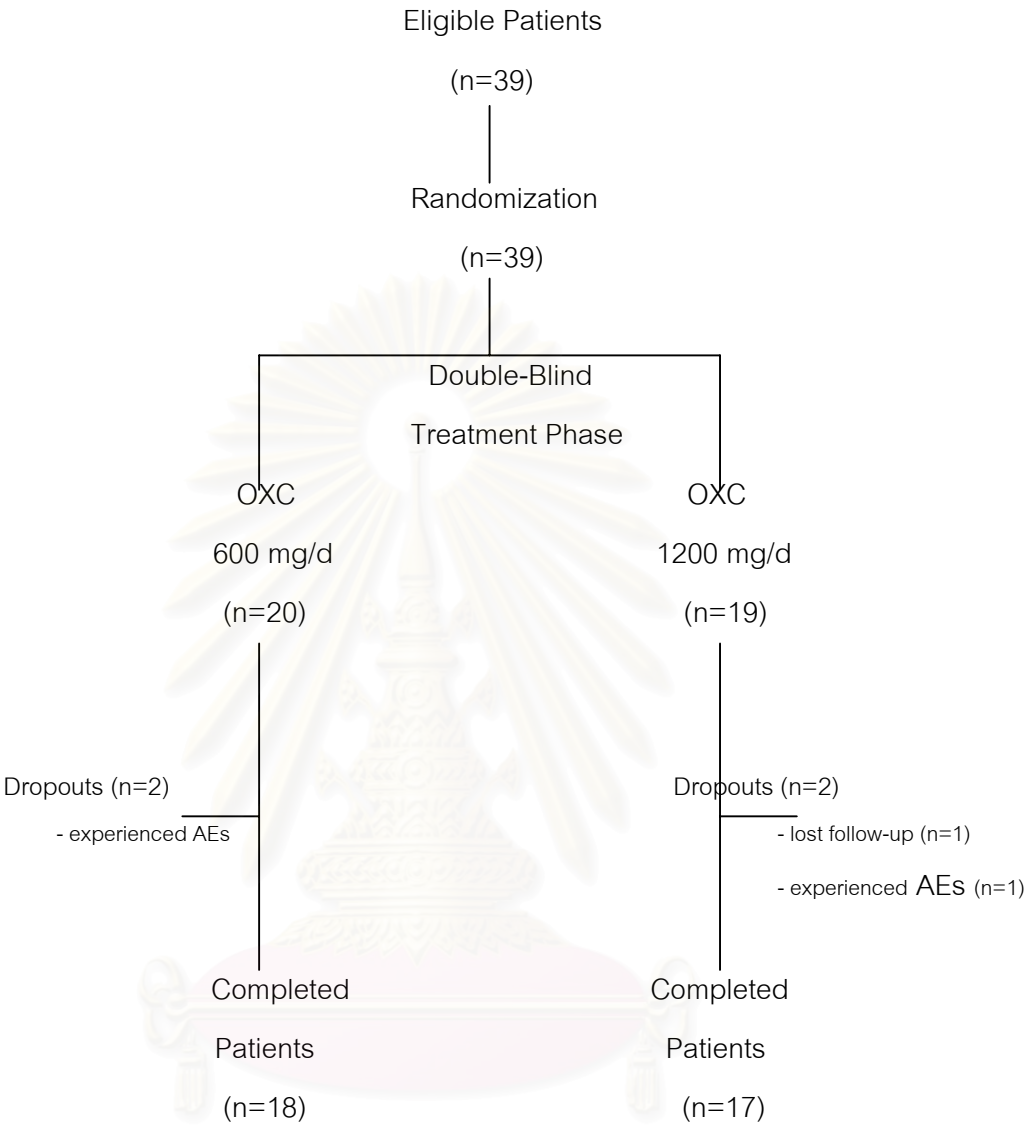

Figure 7. Discontinuation/ Completion summary

OXC = oxcarbazepine

2.2 Efficacy

Primary efficacy end point: percentage change in seizure frequency (PCH)

Thirty-five patients were included in the efficacy analyses. Results of the primary efficacy endpoint are presented in Table 21 and 22. In comparison to baseline period, seizure frequency in treatment period was found to be significantly reduced by OXC in both treatment groups. A 47% median percentage reduction from baseline was observed in patients treated with OXC 600 mg/d compared with a 58% median percentage reduction in patients treated with OXC 1200 mg/d (Figure 8).

Table 21. *Median 28-day seizure frequency for patients receiving 600 mg/d*

	Median seizure frequency		Median
Seizure type	Baseline phase	Treatment period	reduction(%)
All partial (n=18)	4.5	2.5	47%* (p=0.003)
Complex partial (n=15)	3.0	0.8	60%
Simple partial (n=4)	4.5	2.9	22%
SGTC (n=4)	1.3	0.0	100%

* = significant ($p<0.05$)

Table 22. *Median 28-day seizure frequency for patients receiving 1200 mg/d*

	Median seizure frequency		Median
Seizure type	Baseline phase	Treatment period	reduction(%)
All partial (n=17)	4.0	1.8	58%* (p=0.017)
Complex partial (n=15)	3.0	1.1	62%
Simple partial (n=5)	7.0	1.4	79%
SGTC (n=2)	3.0	0.6	89%

* = significant ($p<0.05$)

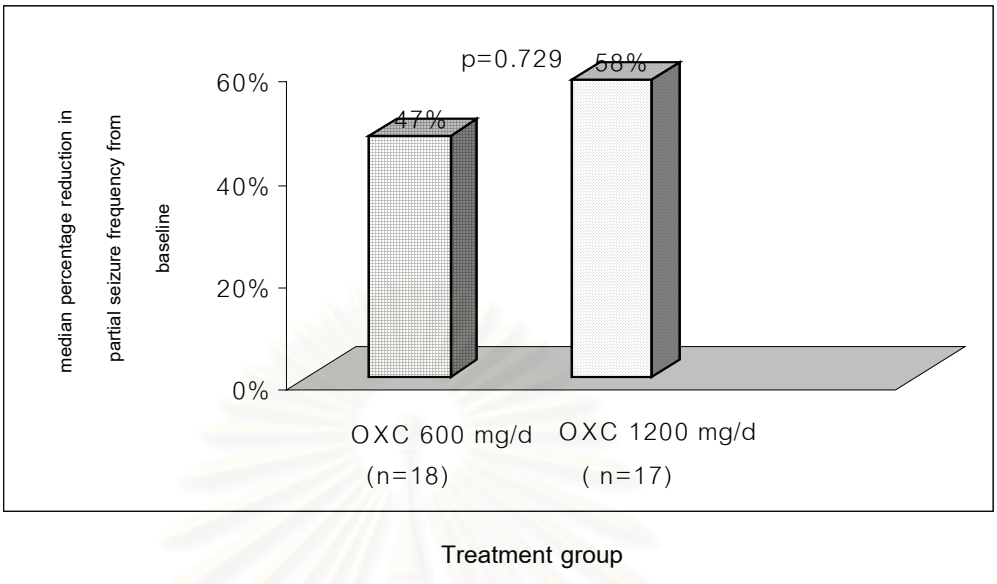

Figure 8. *Median percentage reduction in partial seizure frequency from baseline by 600 and 1200 mg/d OXC group. The p values are for comparison between 2 treatment groups.*

In addition, two dosage treatment groups of OXC demonstrated a reduction from baseline in seizure frequency for all subtype of partial seizure (simple, complex, and partial seizures evolving to secondarily generalized seizures) (Figure 9). Apparently highest response rate was observed on secondarily generalized seizures (Figure 9).

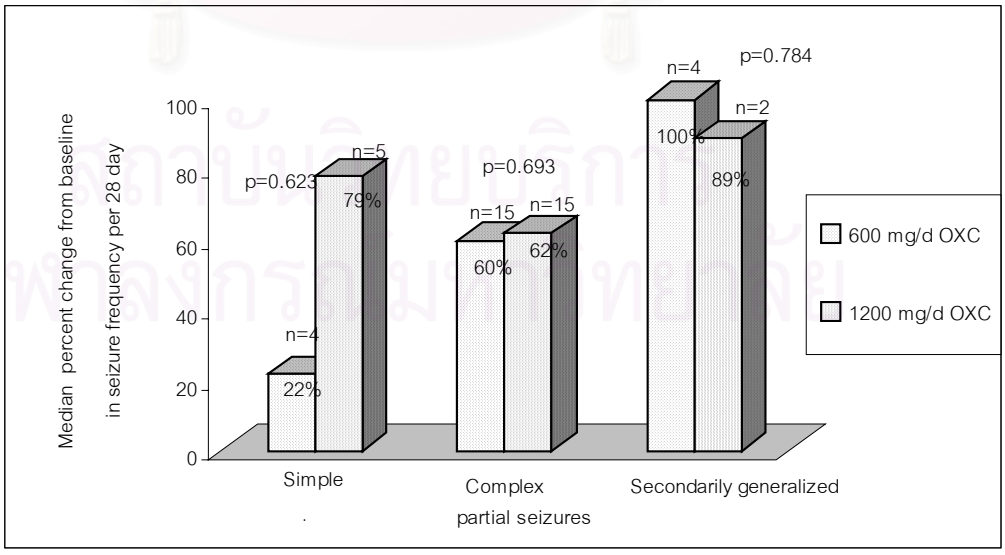

Figure 9. *Median percent change from baseline in seizure frequency per 28 days. For 600 versus 1200 mg/d OXC for all subtype of partial seizures.*

However, the median percentage reduction in all types or each subtype of partial seizure frequency per 28 day during the double-blind treatment phase were not statistically significant different between the group treated with OXC 600 mg/d and the group treated with OXC 1200 mg/d (Figure 8 and 9).

A regression analysis of the percentage change from baseline in seizure frequency (PCH) with dose, sex, age, weight, baseline seizure frequency, and minimum plasma MHD concentration during steady state as explanatory variables demonstrated that only weight was significantly correlated with reduction in seizure frequency ($p = 0.010$).

Efficacy of OXC as add-on therapy to CBZ

The benefit of OXC when added to existing treatment with CBZ was demonstrated when OXC was added to refractory patients who used CBZ (18/35; 51.4%) either monotherapy or polytherapy at baseline. The median percentage reduction in seizure frequency was 58% and 47% in 1200 and 600 mg/d OXC group, respectively. No significant differences between two treatment group was noted (p = 0.587) (Table 23).

Table 23. *Analyses of the percentage change from baseline in 28 days seizure rate (primary efficacy variable) for the completers and for the patients who received CBZ*

Population	Treatment group	
	OXC 600 mg/d	OXC 1200 mg/d
Completers		
N	18	17
Median change in seizure Frequency(%)	- 47%	- 58%
p value	—	0.729
Patients who took CBZ		
N	11	7
Median change in seizure Frequency(%)	- 47%	- 58%
p value	—	0.587

Secondary efficacy endpoint : Response to treatment (responder rate)

Response to treatment was defined as having at least a 50% reduction in 28-day seizure frequency during double-blind treatment compared with baseline. Individual response to treatment for both OXC groups was shown in Table 24. In the protocol analysis for secondary efficacy endpoint, it was found that 44% of patients in the OXC 600 mg/d had at least 50% reduction in seizure frequency comparing to 53% in the OXC 1200 mg/d group, whereas 11% (2/18) in the 600 mg/d group and 12% (2/17) in the 1200 mg/d group became seizure free.

. The proportion of patients who responded to OXC seem to be increased with increasing dose however the 1200 mg/d OXC group did not have a statistically significantly higher percentage of treatment responders (≥50% reduction in seizure frequency) than the 600 mg/d OXC group (p=0.615) (Figure 10).

Paradoxically, seizure frequency was found to be increased (>25% as compared with baseline) in 5 patients. However, it should be noted that severity of seizure was decreased in three of them. One patient receiving OXC 1200 mg/d changed seizure type from complex partial seizures (3 times per 28 day) to simple partial seizures (8 times per 28 days), and a decrease in duration of seizure was found in two patients (one per each treatment group).

As shown in Table 20, among all combination of OXC to others concomitant AEDs in responders group (patients who had ≥50% reduction in seizure frequency), The most effective combination was seen in patients receiving OXC and TPM (75%), others effective combination included OXC and PHT(43%), OXC and CBZ(41%), OXC and VPA(40%), and OXC and PB(20%).

Table 24. Percent reduction from baseline of seizure frequency in the double-blind treatment phase of the responder (≥50% reduction from baseline)

	OXC(mg/d)	
	600	1200
Patient No.	(n=8/18)	(n=9/17)
1)	54%	58%
2)	55%	71%
3)	60%	74%
4)	68%	79%
5)	75%	84%
6)	94%	86%
7)	100%	98%
8)	100%	100%
9)	-	100%
Summary		
≥50% - <75 %	22.0%(n=4)	18.0%(n=3)
≥75% - <90 %	5.5%(n=1)	18.0%(n=3)
≥90% - <100%	5.5%(n=1)	5.0%(n=1)
100%(seizure free)	11.0%(n=2)	12.0%(n=2)
Total	**44.0%(n=8)**	**53.0%(n=9)**
*Increase in seizure frequency	11.0%(n=2)	17.6%(n=3)

* Of 5 patients (14.3%) who had increase in seizure frequency, one patients had changed type of seizure from complex partial seizure(3 times/28days) to simple partial seizure(8 times/28days), and two patients had decrease in duration of seizure.

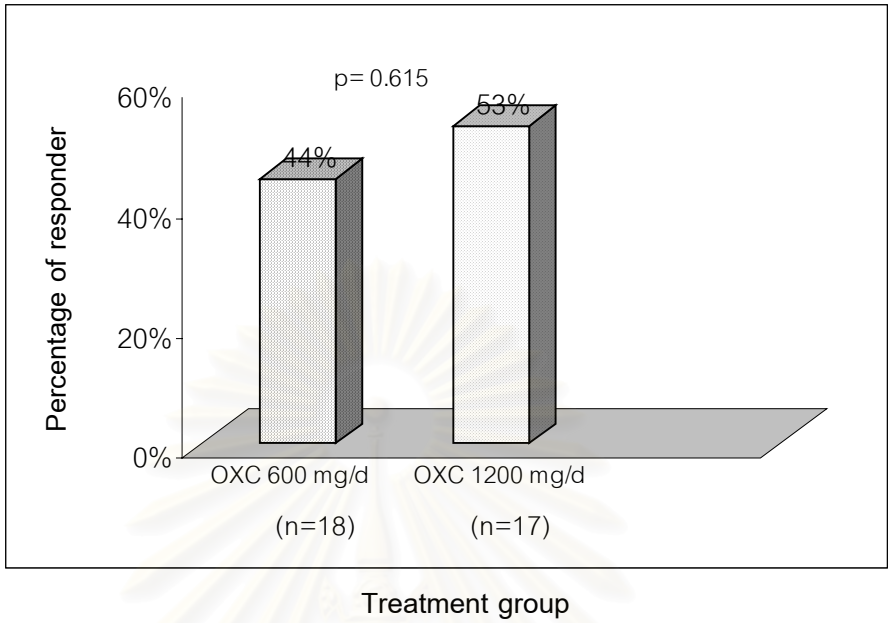

Figure 10. Percentage of responder (≥ 50% reduction in seizure frequency during double- blind treatment from baseline) by 600 and 1200 mg/d OXC treatment group. The p values are for comparison between 2 treatment groups.

2.3 Safety

Report of AEs

AEs, defined as any adverse experienced regardless of its relationship to OXC, that developed during double-blind treatment phase, was interviewed and recorded. They were summarized and being analyzed by intention-to-treat basis including 39 patients (Table 25). The over all incidences of AEs (patients reporting at least one AE) were 85% (33/39) in the OXC 600 mg/d group, and 84% in 1200 mg/d group. These AEs mostly occurred in the first 3 weeks of initial treatment especially in the titration period with mild to moderate in severity and were transient in nature, with tolerance developing in the majority of patient.

The most commonly reported AEs affected patients in both OXC treatment groups involved the nervous system (somnolence, dizziness, ataxia, headache) and the special senses (abnormal vision, diplopia). Dizziness and vomiting are AEs that appeared to increase with increasing dose while the rest are rather comparable.

One patient in the group treated with OXC 1200 mg/d reported rash in week 9 of double-blind treatment phase while receiving CBZ as a concomitant AED, no history of rash occurred while receiving CBZ, this case was considered by physician not to be related to the trial drug and prescribed hydroxycine; 1 day later, the patient returned to normal despite continued OXC.

Three patients (2 in the 600mg/d group and 1 in the 1200mg/d OXC group) discontinued prematurely due to AEs. An increase in seizure frequency (30 seizures in a day despite baseline seizure frequency was 5 seizures/28 days) was observed in one patient receiving OXC 600 mg/d. It is noteworthy that all of them were taking OXC with more than one concomitant AEDs while all patients who did not experience AEs are those receiving OXC with only one concomitant AED. Discontinuation occurred within 3 weeks of initiation trial

treatment. No patients were discontinued prematurely because of abnormal laboratory value.

AEs	OXC (mg/d)		total
	600 (n=20) n(%)	1200 (n=19) n(%)	n(%)
Number reporting an AE	17(85%)	16(84.2%)	33(84.6%)
Nervous system			
Somnolence	10(50%)	8(42.1%)	18(46%)
Ataxia	7(35%)	5(26.3%)	12(30.8%)
Dizziness	3(15%)	8(42.1%)	11(28.2%)
Headache	3(15%)	3(15.8%)	6(15.4%)
Special senses			
Abnormal vision	4(20%)	3(15.8%)	7(18%)
Diplopia	1(5%)	1(5.3%)	2(5.1%)
Digestive system			
Vomiting	0(0%)	2(10.5%)	2(5.1%)
Nausea	1(5%)	1(5.3%)	2(5.1%)
Body as a whole			
Fatigue	2(10%)	1(5.3%)	3(7.7%)
Skin			
Rash	0(0%)	1(5.3%)	1(2.5%)

Table 25. *Incidence of AEs reported during double-blind treatment in each treatment group (all patients)*

Laboratory assessment of clinical safety

Routine clinical laboratory evaluations were performed at baseline and at specified visit during the double-blind treatment phase. The mean differences between baseline and postrandomized values did not reveal any clinically significant trends in either dosage group. The mean serum sodium levels remained unchanged following treatment with OXC in two dosage group (for 1200 mg/d OXC group; baseline mean [median], 136.37 mEq/L [137 mEq/L]; study end mean [median], 136.08 mEq/L [137.5 mEq/L]; and for 600mg/d OXC group; baseline mean [median], 137.93 mEq/L [138.6 mEq/L]; study end mean [median], 136.91 mEq/L [138.9 mEq/L]). However 2 patients in 600 mg/d group (140 mEq/L at baseline /129.8 mEq/L at treatment, 137.9/125) and one (130.2/125.5) in 1200 mg/d group tended to decrease serum sodium levels, Two patients (1 per each treatment group) receiving CBZ as a concomitant AED and one receiving NSAID(diclofenac) as a concomitant drug. No patient had treatment-emergent, markedly abnormal values at two or more visits for any of the following laboratory parameters: basophils, monocytes, red blood cell count, albumin, total bilirubin, blood urea nitrogen, potassium, creatinine, fasting glucose, SGOT, and SGPT.

2.4 Plasma AEDs concentrations

Plasma MHD concentrations

Mean trough plasma concentrations of MHD at steady state were linearly correlated with the OXC dose (p=0.000). Mean trough plasma was 6.77 μg/ml and 12.46 μg/ml in the 600mg/d and the 1200 mg/d group, respectively. A significant correlation was not observed between trough MHD concentrations and primary efficacy parameter (PCH). Of patients who had ≥ 50% reduction in partial seizure frequency per 28 days (responder), mean trough plasma were 7.26 and 13.97 μg/ml in the 600 and 1200 mg/d, respectively whereas they were 6.39 and 10.75 μg/ml in non-responder group.

Interactions with concomitant AEDs

Concomitant AEDs plasma concentrations both treatment groups were unaffected by coadministration of OXC and fluctuated by ≤ 20% in >85% of patients.

CHAPTER V

DISCUSSION AND CONCLUSION

In general, therapy of epilepsy should be initiated with monotherapy however, if monotherapy is not effective in controlling seizures, a rational approach using more than one AED, or combined AEDs, should be used (Leppik, 2000). In the present study, efficacy and safety of OXC which is a newly registered AED in Thailand, was evaluated in Thai epileptic patients as add-on therapy. Though the add-on therapy is the standard designs to evaluate the safety and efficacy of new AEDs, it has limitations which include the refractory nature of the patient population studied, the potential for pharmacokinetic and pharmacodynamic interactions between the study drug and the baseline AEDs, the AEDs under test are frequently underdosed while the adverse events are generally overestimated. Despite these limitations, adjunctive therapy trials were successful in proving the efficacy of the newer AEDs that were recently licensed. Such adjunctive therapy designs are also considered a necessary step before proceeding to monotherapy trails in the patient population. Usually, partial epilepsies represent the first target for the trial, since among all types of epileptic seizures, partial seizures are the most frequent, and difficult to control (Sachdeo, 2000).

Since this is the first trial of OXC in Thai epileptic patients and based on the ground that 600 mg/d is the minimum recommended effective dosage for OXC as adjunctive therapy in adults (Barce et al, 2000), efficacy of OXC 600 and 1200 mg/d were compared in the present study.

The results of this trial clearly demonstrated that adjunctive therapy with OXC at dosage 600 and 1200 mg/d (administered in divided doses twice daily) were effective in Thai patients with uncontrolled partial seizures with or without secondarily generalized seizures. About half of each OXC treatment group showed a significant decrease in

seizure frequency per 28 days (47% in the 600 mg/d group (p=0.003) and 58% (p=0.017) in the 1200 mg/d group) in double-blind treatment phase. Accordingly, the percentage of treatment responders (50% or greater reduction in seizure frequency from baseline) was also observed (44% in the 600mg/d group and 53% in the 1200 mg/d group). Both of efficacy variables (PCH and responder rate) seem to increase with increasing dose, however no significant difference was identified between the two dose of OXC. Analysis by seizure subtype revealed a decrease in the number of seizures for all subtypes, however differences between the two doses were also not significant.

Larger number of patients was needed to demonstrate increasing efficacy of higher dose has been advocated by Kramer et al. (1993). Thus the present study provides the evidence that, in line with previous report (Barce et al., 2000) OXC 600 mg/d which is the minimum effective dose was effective in Thai epileptic patients as add-on therapy. Furthermore increasing efficacy of OXC 1200 mg/d, though not statistically significant, was noted.

Comparatively, OXC in the doses tested (600 and 1200 mg/d) appear to exhibit higher efficacy than those previously reported in non-Asian patients (Barce et al., 2000). This may be accounted by firstly, a lower median baseline seizure frequency of the patients (4-4.5 seizures/28 days in this trial comparing with 9-10 seizures/28 days in the previous trial), this assumption was supported by the study (Brodie and Kwan, 2002) which reported that patients with a high number of seizures were less likely to be controlled; secondly a lower mean body weight of the patients (60 kg in this trial comparing with 71kg in the previous trial). As clearance and volume of distribution were significantly related to body weight, so lower clearance and volume of distribution are expected in the study population and this may explain also rather high trough plasma concentration of MHD in the present study (6.77μg/mL) comparing to 4.7μg/mL from OXC 600 mg/d (Barce et al., 2000) as previous reported. Similarly, clinical trial of TPM in adult study Chinese patients (Der-Jen Yen et al., 2000) demonstrated lower minimum

effective dosage than that required by non-Asian patients (Sharief et al., 1996), based on Chinese patients would have a smaller body weight than non-Asians. In addition, a regression analysis in this trial shown that weight was significantly correlated with reduction in seizure frequency.

Generally, combinations of AEDs showing different and multiple mechanisms of action are more likely to result in synergy than drugs sharing similar mechanism (Czuczwar, 2000). It was noted that more patients become seizure free with the add-on combination included a sodium channel blocker and a drug with multiple mode of action than with other combinations (Kwan and Brodie, 2000a). Synergy between TPM and CBZ has been shown by isobolographic analysis (Czuczwar, 2000). In line with these, it was found that an addition of OXC, a sodium channel blocker (Brodie and Kwan, 2002), to patients currently used TPM which processes multiple mechanisms of action (Brodie and Kwan, 2002) was the most effective combination with 75% responder (Table 20). Additionally, based on the result that improving efficacy was exhibited by a combination of OXC and CBZ (Table 23), it is suggestive that OXC may have some other mechanisms than blocking of sodium channel.

The percentage of patients who reported one or more AEs are not different between 2 dosage groups (85% for the 600 mg/d and 84% for the 1200 mg/d group). The incidences of AEs as well as premature discontinuations due to AEs were apparent during the first 3 weeks of double-blind treatment phase. Most of AEs were rated as mild to moderate in severity and were transient in nature, with tolerance developing in the majority of patients. These incidences were similar to the previous clinical study (Barce et al., 2000). In clinical practice, these high AEs incidences potentially can be avoided or reduced by lower starting dose, slower rate of titration and lowering dosage of baseline AEDs when OXC is being introduced (Pellock, 2002). In addition, some patients may tolerate the drug better when it is given thrice-daily (Beydoun and Kutluay, 2002).

In line with previous report that AEs that were most frequently associated with OXC treatment and appeared to be dose related were the effects on central nervous system and digestive system, the AEs that were most frequently reported hereby were central nervous system-related e.g. somnolence, ataxia, dizziness, and headache and abnormal vision. Furthermore the AEs that appeared to be dose related were dizziness and vomiting.

Based on clinical experience, OXC adjunctive therapy can be initiated at 300 mg/d (150mg b.i.d.), 4 weeks to target dose (Beydoun and Kutluay, 2002; Pellock, 2002) or 300 mg/day (150mg b.i.d.), increments of 300-600 mg at approximately weekly intervals (Glauser, 2001) or starts with 150 mg/d and the daily dose increased by 150mg/d every 2-3 days (Schmidt and Sachdeo, 2000). The AEs causing premature discontinuations were dizziness, headache, somnolence and abnormal vision.

It is noteworthy that all of patients who prematurely discontinued were taking OXC with more than one concomitant AEDs while all patients who did not experience AEs are the patients receiving OXC with only one concomitant AED. Thus, it implies that the preexisting total AED drug load, rather than any specific background AEDs or interactions with any one specific AEDs, resulted in most AEs and premature discontinuations incidences.

As with CBZ, the incidence of hyponatremia has been reported with OXC use (Nielsen et al., 1988). Hyponatremia was usually asymptomatic and appeared within the 3 months of treatment (Van Amelsvoort et. al, 1994). It is rarely accompanied by clinical symptomatology. Experience from clinical trails has revealed a very low (0.41%) incidence of two or more consecutive serum values of less than 125 mEq/L. Furthermore, it has been shown that serum sodium levels returned to normal when the OXC dosage was reduced, discontinued, or the patient's fluid intake was restricted (Chadwick and Privitera, 1999).

In this trial, no patient demonstrated a clinical significant lowered plasma sodium level (plasma sodium < 125 mEq/L) on consecutive visit during the double blind treatment phase. However, a distinct lowered plasma sodium level that might be related to OXC treatment was observed in three patients. All of them receiving CBZ (one per each group) and NSAIDs; Diclofenac (one from 600 mg/d OXC), which are known to cause hyponatremia, as a concomitant AED. It might therefore be prudent to check a baseline sodium level prior to initiating OXC therapy, especially in patients receiving concomitant sodium-wasting drugs, such as diuretics, antipsychotics, antidepressants, NSAIDs and CBZ (Sachdeo et, al., 1999).

Mean trough plasma concentrations (Cmin) of MHD at steady state were linearly correlated with the OXC dose (6.77 μg/mL for the 600 mg/d group and 12.46 μg/mL for the 1200 mg/d group)(p=0.000). These results are in line with other pharmacokinetic studies (Dickinson et al., 1989; Lloyd et al., 1994) which provided evidence that, there was a linear relationship between oral OXC dosages and plasma MHD concentrations in healthy volunteers and in patients with epilepsy who were receiving OXC monotherapy or polytherapy (Cloyd, 2000). Thus routine monitoring serum concentration of OXC or its active metabolite (MHD) is not necessary, unless in case of checking for compliance or toxicity (Dieter Schmidt and Rajesh Sachdeo, 2000).

In the present study, therapeutic plasma range of MHD in that patients cannot be established by the fact that there was no correlation between efficacy and the serum levels of MHD, albeit, higher dose give higher plasma concentration. Interestingly, it was found that mean trough plasma levels of MHD (Cmin) in responders were higher than those in non-responder (7.26 and 13.97 μg/mL in the 600 and 1200 mg/d group, respectively vs 6.39 and 10.75 μg/mL in non-responder). Taken into consideration that therapeutic range of MHD was about 12-35 μg/mL (Bill et al., 1997), it can be anticipated that higher dose than 1200 mg/d of OXC could be applied to achieve better control, if the patients can tolerate AEs.

Finally, OXC therapy in this trial did not adversely affected hematologic, renal and hepatic function or causing hypersensitivity reactions like those reported in previously in OXC-controlled clinical trials (Barce et al, 2000 ; Glauser et al., 2000).

In conclusion, the present study demonstrated that efficacy of OXC 600 and 1200 mg/d as add-on therapy in Thai adult epileptic patients with uncontrolled partial seizures, including the seizure subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures. Comparatively, higher percentage of reduction in seizure frequency as well as higher rate of responder ($\geq$50% seizure reduction) were exhibited by OXC 1200 mg/d, however with no statistical significant different from those of 2 dosage groups. In addition, while exhibiting mild to moderate degree, transient in nature and comparable adverse effect profile with those previously reported in non-Asian patients, OXC was found to be more effective in controlling seizure. More informations on efficacy and safety of different doses of OXC especially lower than 600 mg/d or higher than 1200 mg/d as add-on therapy, or monotherapy study in Thai epileptic patients are further required.

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APPENDICES

Baseline demographic and concomitant AEDs characteristics of 39 randomized patients

Patient No.	Dose (mg/d)	Sex	Age (years)	Weight (kg)	Concomitant AEDs use and dosage regimen (mg/d)					
					PHT	PB	CBZ	VPA	TPM	LTG
1	600	M	26	62				2000		
2	600	M	26	55	300		1300	1500		
3	600	M	33	52	300		1400			
4	600	F	31	48			1300	1500		
5	600	F	36	70				2000		
6	600	F	36	50	300	120	800			
7	600	M	37	54			900	1000		
8	600	F	18	65	300		1200	1250		
9	600	F	28	55			1400			
10	600	M	24	50			1700			100
11	600	M	44	77			1200	1500		
12	600	F	39	56		120		1750		
13	600	M	37	78		120	800			
14	600	M	36	76	300			1750		
15	600	M	33	55	400					
16	600	F	35	42			1600			
17	600	M	19	44			800	1000		200
18	600	M	25	60	300					
19	600	F	20	55				1000		
20	600	M	25	63	200		1400		350	

Continued .....

Baseline demographic and concomitant AEDs characteristics of 39 randomized patients (Continued.)

Patient No.	Dose (mg/d)	Sex	Age (years)	Weight (kg)	Concomitant AEDs use and dosage regimen (mg/d)					
					PHT	PB	CBZ	VPA	TPM	LTG
21	1200	M	25	57	400	120				
22	1200	M	41	76					250	
23	1200	F	43	50		120				
24	1200	M	38	55	300					
25	1200	F	29	56	200	120	1200			
26	1200	F	36	50			1200			
27	1200	M	25	71			1200			
28	1200	F	33	80			600	1500		
29	1200	F	28	60	200	120	1400			
30	1200	F	26	46	300					
31	1200	F	27	51		120				
32	1200	M	39	80				2000		
33	1200	M	36	60			1000			
34	1200	M	33	60	300	60	800			
35	1200	F	35	57			1400	500	50	
36	1200	F	18	60			1200			
37	1200	M	32	80					200	
38	1200	F	37	70				2000		
39	1200	F	44	53		120				

Abbreviation : AEDs= anti-epileptic drugs, PHT= Phenytoin, CBZ=Carbamazepine, VPA= Valproic acid ,PB= Penobarb, LTG= Lamotrigine, TPM= Topamax, M= Male, F=Female

Therapeutic dose: CBZ = 400-1800 mg/d ; VPA = 500-2500 mg/d
LTG = 300-500 mg/d ;TPM= 200-600 mg/d
PHT = 300-500 mg/d ; PB = 60-240 mg/d

Characteristics and frequency of partial seizures, and %PCH in patients who receiving 600 mg/d OXC group

No.	Baseline				treatment				*%PCH
	Average seizure frequency(times/28days)				Average seizure frequency (times/28days)				
	SPS	CPS	PWSG	ALL	SPS	CPS	PWSG	ALL	
1		3.50		3.50		0.86		0.86	↓75%
2		8.00		8.00		2.57		2.57	↓68%
3¶			5.00	5.00	-	-	-	-	-
4¶		2.00		2.00	-	-	-	-	-
5		2.00		2.00		0.00		0.00	↓100%
6	30.00	28.00		58.00	31.00	21.00		52.00	↓10%
7		3.00		3.00		4.26		4.26	↑42%
8		8.50		8.50		8.30		8.30	↓2%
9		2.00		2.00		1.07		1.07	↓47%
10		3.00		3.00	0.27	2.13		2.40	↓20%
11		2.00		2.00		0.00		0.00	↓100%
12		14.00		14.00	8.29	0.28		8.57	↓39%
13	4.00		1.00	5.00	1.44	0.86	0.00	2.30	↓54%
14		1.00	1.50	2.50		1.33	0.00	1.33	↓47%
15	3.00		1.00	4.00	2.95		0.00	2.95	↓26%
16	5.00	2.00		7.00	2.90	0.30		3.14	↓55%
17			6.00	6.00			8.00	8.00	↑33%
18		10.00		10.00		0.57		0.57	↓94%
19		5.00		5.00	0.55	2.50		3.05	↓39%
20		2.00		2.00		0.80		0.80	↓60%

Abbreviations: SPS= Simple partial seizures, CPS= Complex partial seizures, PWSG= Partial seizures with secondarily generalized tonic-clonic seizure

*%PCH= 100×(T-B)/B where T is the number of seizures per 28 days during treatment and B is the number of seizures per 28 days during the baseline phase

¶patient No. 3 and 4 discontinued prematurely from the trial

Characteristics and frequency of partial seizures, and %PCH in patients who receiving 1200 mg/d OXC group

No.	Baseline				treatment				%PCH
	Average seizure frequency(times/28days)				Average seizure frequency(times/28days)				
	SPS	CPS	PWSG	ALL	SPS	CPS	PWSG	ALL	
21		20.00		20.00		3.20		3.20	↓84%
22	12.00	2.40		14.40	0.00	0.29		0.29	↓98%
23		7.00		7.00	0.66	4.34		5.00	↓29%
24		2		2.00		1.80		1.80	↓10%
25		3.00		3.00	8.86	0.00		8.86	↑155%
26	1.00	2.00		3.00	0.00	0.86		0.86	↓71%
27		2.00		2.00		0.00		0.00	↓100%
28		4.00		4.00		1.70		1.70	↓58%
29		10.00		10.00		1.43		1.43	↓86%
30		2.00		2.00		0.53		0.53	↓74%
31		2.00		2.00		3.00		3.00	↑50%
32	7.00		5.00	12.00	1.45		1.10	2.55	↓79%
33		1.00	1.00	2.00	0.29	1.14	0.00	1.43	↓28.5%
34¶		2.00		2.00	-	-	-	-	-
35	14.00			14.00	19.43			19.43	↑39%
36¶	9.00	11.00		20.00	-	-	-	-	-
37		3.00		3.00		0.00		0.00	↓100%
38	1.00	3.00		4.00	1.43	1.14		2.57	↓36%
39		20.00		20.00		12.86		12.86	↓36%

Abbreviations: SPS= Simple partial seizures, CPS= Complex partial seizures, PWSG= Partial seizures with secondarily generalized tonic-clonic seizure

*%PCH= 100×(T-B)/B where T is the number of seizures per 28 days during treatment and B is the number of seizures per 28 days during the baseline phase

¶patient No. 34 and 36 discontinued prematurely from the trial

Blood levels of concomitant AEDs in randomized patients who receiving 600 mg/d OXC

No	Baseline(visit 1)				Visit 2				Visit 3				Visit 4			
	AEDs (μg/ml)				AEDs (μg/ml)				AEDs (μg/ml)				AEDs (μg/ml)			
	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA
1				74.36				67.07				66.26				74.79
2	7.37		7.31	89.13	9.68		9.23	69.24	12.07		4.31	100.73	7.71		4.5	61.56
3	19.64	-	7.60	-	-		-		-		-		-		-	
4	-	-	5.06	48.9			-	-			-	-			-	-
5				49.18				-				43.53				49.81
6	21.33	9.3	4.27		30.04	30.16	0.54		25.72	30.69	3.55		10.22	22.81	2.41	
7			12.04	75.55			4.19	63.43			4.89	51.73			4.7	49.46
8	5.7		4.43	41.59	6.34		3.76	64.88	7.74		3.81	59.23	4.47		2.48	43.25
9			5.95				7.94				7.94				3.83	
10			8.25				7.20				5.53				4.52	
11			4.72	68.14			5.54	89.31			4.98	74.13			4.53	51.58
12		11.48		52.13		9.59		83.84		-		-		9.82		62.52
13		21.20	7.84			17.53	6.33			13.75	4.53			16.58	5.56	
14	19.9			49.83	19.31			12.48	-			-	18.5			49.50
15	16.24				22.85				11.17				14.18			
16			6.22				5.52				5.63				5.28	

Continued…….

Blood levels of concomitant AEDs in randomized patients who receiving 600 mg/d OXC (Continued)

No	Baseline(visit 1)				Visit 2				Visit 3				Visit 4			
	AEDs (μg/ml)				AEDs (μg/ml)				AEDs (μg/ml)				AEDs (μg/ml)			
	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA
17			5.56	42.46			5.03	40.75			5.32	50.65			4.06	37.95
18	21.46				20.98				25.85				31.86			
19				51.93				-				72.73				57.10
20	3.00		10.09		2.89		8.06		-		-		2.5		7.07	

Blood levels of concomitant AEDs in randomized patients who receiving 1200 mg/d OXC

No	Baseline(visit 1)				Visit 2				Visit 3				Visit 4			
	AEDs (μg/ml)				AEDs (μg/ml)				AEDs (μg/ml)				AEDs (μg/ml)			
	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA
21	9.12	7.76			10.33	6.53			8.18	6.05			7.3	5.71		
22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23		20.35				23.61				20.42				21.18		
24	14.69				19.24				15.11				29.70			
25	2.53	20.74	5.42		3.59	22.11	3.59		4.24	19.49	3.9		5.99	21.82	4.16	
26			9.66				9.56				5.65				5.8	
27			9.79				7.47				8.22				6.87	
28			8.36	60.14			-	-			7.87	79.07			7.78	73.84
29	2.36	21.86	5.25		2.16	22.24	5.13		6.94	24.23	4.47		7.09	20.18	3.69	
30	15.61				11.75				12.13				23.47			
31		30.77				20.32			-	-				16.28		
32				78.37				88.27				-				84.22
33			11.49				7.66				5.16				4.89	
34	11.56	10.55	2.5		-	-	-		-	-	-		-	-	-	
35			10.5	39.31			5.29	38.59			4.15	30.99			2.46	27.36
36			4.69				-				–				–	

Continued…….

Blood levels of concomitant AEDs in randomized patients who receiving 1200 mg/d OXC (Continued)

No	Baseline(visit 1)				Visit 2				Visit 3				Visit 4			
	AEDs (μg/ml)				AEDs (μg/ml)				AEDs (μg/ml)				AEDs (μg/ml)			
	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA	PHT	PB	CBZ	VPA
37	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
38				80.74				78.94				74.32				72.15
39		18.34				21.60				19.89				20.06		

Abbreviation : AEDs= anti-epileptic drugs, PHT= Phenytoin, CBZ= carbamazepine, VPA= valproic acid ,PB= phenobarb

Therapeutic blood level : CBZ = 4-12 μg/ml PHT = 10-20 μg/ml

PB = 20-40 μg/ml VPA = 50-100 μg/ml

Baseline clinical blood chemistry characteristics of 39 randomized patients:

Subject No.	Dosage group (mg/d)	FBS mmol/L * (3.8-6.1)	SGOT U/L * (0-37)	SGPT U/L * (0-40)	ALP U/L * (39-117)	BUN mmol/L * (2.14-7.14)	CrCl umol/L * (62-124)	Na^+ mEql/L * (135-145)	K^+ mEq/L * (3.5-5)
1	600	4.6	19	13	43	3.5	105	139	4.2
2	600	4.8	17	9	61	2.8	72	134	4.3
3	600	4.3	19	15	106	4.9	75	140	3.58
4	600	5.6	22	20	47	3.1	62	137.2	3.81
5	600	5.5	43	69	55	3.0	57	139.6	4.19
6	600	3.4	19	17	78	2.6	64	138.4	4.03
7	600	4.6	20	19	73	3.2	90	141.0	3.78
8	600	4.6	31	48	82	4.3	66	135.3	4.37
9	600	5.1	23	12	43	3.7	65	140.2	4.49
10	600	4.7	18	29	61	3.0	79	138.8	4.52
11	600	5.3	15	11	61	4.1	86	141.5	4.48
12	600	4.7	37	22	90	3.9	94	137.9	4.89
13	600	4.6	20	19	94	4.2	92	135.7	4.12
14	600	5.9	23	26	77	4.6	83	138.4	4.25
15	600	4.0	20	27	90	4.3	78	135.0	4.89
16	600	5.0	16	9	82	3.7	67	138	3.7
17	600	4.8	13	7	116	2.1	54	135.1	3.6

Continued……

Baseline cinical blood chemistry characteristics of 39 randomized patients (Continued):

Subject No.	Dosage group (mg/d)	FBS mmol/L *(3.8-6.1)	SGOT U/L *(0-37)	SGPT U/L *(0-40)	ALP U/L *(39-117)	BUN mmol/L *(2.14-7.14)	CrCl umol/L *(62-124)	Na^+ mEq/L *(135-145)	K^+ mEq/L *(3.5-5)
18	600	4.4	29	30	85	4.5	80	139.4	4.03
19	600	4.9	15	13	117	5.0	65	135.9	3.84
20	600	5.3	13	23	102	4.1	87	135.7	3.58
21	1200	4.6	28	37	60	2.3	74	135	3.13
22	1200	4.9	14	20	91	5.91	114	138.4	3.95
23	1200	4.4	33	50	71	4.5	68	137	3.77
24	1200	5.7	29	47	116	2.5	71	139.6	3.91
25	1200	5.1	22	21	73	4.2	58	135.8	4.36
26	1200	4.8	21	21	57	3.8	60	139.4	4.10
27	1200	4.4	27	33	72	2.5	75	142.5	4.35
28	1200	3.9	12	10	60	1.9	52	136.8	4.04
29	1200	3.3	18	12	81	2.2	62	135.0	3.59
30	1200	5.9	16	16	128	2.5	67	137.4	3.6
31	1200	3.8	27	31	51	4.0	65	136.9	3.89
32	1200	3.6	64	34	118	3.3	80	130.1	2.99
33	1200	5.2	19	26	91	2.0	69	130.2	4.63
34	1200	4.4	21	30	89	3.2	85	144.9	4.17

Continued……

Baseline cinical blood chemistry characteristics of 39 randomized patients (Continued):

Subject No.	Dosage group (mg/d)	FBS mmol/L ✱(3.8-6.1)	SGOT U/L ✱ (0-37)	SGPT U/L ✱(0-40)	ALP U/L ✱ (39-117)	BUN mmol/L ✱ (2.14-7.14)	CrCl umol/L ✱ (62-124)	Na^+ mEq/L ✱ (135-145)	K^+ mEq/L ✱ (3.5-5)
35	1200	4.7	14	6	64	2.1	56	130.5	3.82
36	1200	4.3	18	22	75	3.8	61	143.5	4.17
37	1200	5.3	18	26	104	5.1	93	138.3	4.2
38	1200	4.6	18	19	33	5.2	70	138.3	3.9
39	1200	5.1	17	12	71	3.6	68	138.1	4.48

✱= Normal Range

Clinical blood chemistry characteristics of 39 randomized patients at follow up visit 2

Subject No.	Dosage group (mg/d)	FBS mmol/L * (3.8-6.1)	SGOT U/L * (0-37)	SGPT U/L * (0-40)	ALP U/L * (39-117)	BUN mmol/L * (2.14-7.14)	CrCl umol/L * (62-124)	Na^+ mEq/L * (135-145)	K^+ mEq/L * (3.5-5)
1	600	5.2	33	30	45	4.2	109	139.3	4.24
2	600	4.6	19	15	74	4.9	81	134.8	4.34
3	600	-	-	-	-	-	-	-	-
4	600	-	-	-	-	-	-	-	-
5	600	-	-	-	-	-	-	-	-
6	600	4.1	20	22	73	1.9	65	138.1	3.85
7	600	5.4	21	21	60	4.2	93	139.5	3.83
8	600	4.6	41	52	82	3.0	69	138.3	4.54
9	600	4.6	21	22	53	3.2	64	129.5	3.71
10	600	4.4	18	27	69	2.4	77	135.4	4.39
11	600	5.2	15	12	49	3.9	89	143.9	4.75
12	600	-	-	-	-	-	-		-
13	600	5.4	19	20	91	3.7	98	139.6	3.91
14	600	4.4	19	20	78	2.9	78	137.2	3.89
15	600	4.3	23	36	86	3.8	78	137.4	3.97
16	600	4.5	16	9	69	2.2	66	136.8	3.89

Continued .....

Clinical blood chemistry characteristics of 39 randomized patients at follow up visit 2 (Continued):

Subject No.	Dosage group (mg/d)	FBS mmol/L * (3.8-6.1)	SGOT U/L * (0-37)	SGPT U/L * (0-40)	ALP U/L * (39-117)	BUN mmol/L * (2.14-7.14)	CrCl umol/L * (62-124)	Na^+ mEq/L * (135-145)	K^+ mEq/L * (3.5-5)
17	600	5.8	18	13	96	2.1	66	132.6	3.59
18	600	5.1	28	27	79	3.1	79	138.0	4.05
19	600	-	-	-	-	-	-	-	-
20	600	-	-	-	-	-	-	-	-
21	1200	4.7	22	31	72	1.7	72	134.7	3.09
22	1200	4.9	17	25	88	4.4	101	136.5	3.73
23	1200	4.2	37	52	65	4.2	68	139.5	4.11
24	1200	5.8	28	38	138	2.5	74	138.6	3.83
25	1200	4.3	23	21	67	5.2	62	137.0	4.43
26	1200	4.9	22	18	61	3.4	56	137.0	3.56
27	1200	4.4	24	26	74	3.9	71	136.2	3.75
28	1200	-	-	-	-	-	-	-	-
29	1200	-	-	-	-	-	-	-	-
30	1200	5.0	19	20	141	2.9	67	142.0	3.64
31	1200	-	-	-	-	-	-	-	-
32	1200	-	-	-	-	-	-	-	-

Continued.....

Clinical blood chemistry characteristics of 39 randomized patients at follow up visit 2 (Continued):

Subject No.	Dosage group (mg/d)	FBS mmol/L *(3.8-6.1)	SGOT U/L * (0-37)	SGPT U/L *(0-40)	ALP U/L * (39-117)	BUN mmol/L * (2.14-7.14)	CrCl umol/L * (62-124)	Na^+ mEq/L * (135-145)	K^+ mEq/L * (3.5-5)
33	1200	5.7	17	25	82	4.8	79	122.2	3.93
34	1200	-	-	-	-	-	-	-	-
35	1200	3.9	15	7	67	2.7	60	129.4	3.93
36	1200	-	-	-	-	-	-	-	-
37	1200	5.7	25	44	91	5.4	102	140.7	3.65
38	1200	4.8	20	27	48	3.5	76	139.6	4.11
39	1200	4.9	21	15	66	4.8	71	136.5	3.72

*= Normal Range

Clinical blood chemistry characteristics of 39 randomized patients at follow up visit 3:

Subject No.	Dosage group (mg/d)	FBS mmol/L * (3.8-6.1)	SGOT U/L * (0-37)	SGPT U/L * (0-40)	ALP U/L * (39-117)	BUN mmol/L * (2.14-7.14)	CrCl umol/L * (62-124)	Na^+ mEq/L * (135-145)	K^+ mEq/L * (3.5-5)
1	600	5.6	35	21	52	4.3	105	135.5	4.43
2	600	4.6	18	13	63	2.6	73	130.7	4.62
3	600	-	-	-	-	-	-	-	-
4	600	-	-	-	-	-	-	-	-
5	600	4.9	59	77	58	2.3	52	139.9	3.9
6	600	2.8	17	14	86	3.2	65	137.8	4.59
7	600	4.7	18	18	61	2.9	85	139.5	4.41
8	600	5.1	31	49	77	5.7	74	134.3	3.66
9	600	5.1	24	18	59	3.6	63	128.6	4.0
10	600	4.1	18	30	58	1.7	70	134.5	3.73
11	600	4.5	17	17	53	5.2	79	141.2	4.69
12	600	3.5	31	13	83	3.6	88	118.9	4.74
13	600	6.1	17	21	88	3.4	91	139.7	3.25
14	600	4.4	19	20	78	2.9	78	137.2	3.89
15	600	4.4	21	28	79	3.5	74	138.6	3.68
16	600	4.5	15	9	73	1.9	61	134.6	4.18
17	600	4.5	14	9	100	3.2	49	133.2	3.54

Continued……

Clinical blood chemistry characteristics of 39 randomized patients at follow up visit 3(Continued):

Subject No.	Dosage group (mg/d)	FBS mmol/L * (3.8-6.1)	SGOT U/L * (0-37)	SGPT U/L * (0-40)	ALP U/L * (39-117)	BUN mmol/L * (2.14-7.14)	CrCl umol/L * (62-124)	Na^+ mEq/L * (135-145)	K^+ mEq/L * (3.5-5)
18	600	5.5	23	22	68	2.5	83	138.3	3.87
19	600	3.0	13	12	148	4.1	64	141.4	3.81
20	600	4.6	14	20	99	3.9	84	137.1	3.7
21	1200	4.2	23	44	71	2.3	74	137.3	3.61
22	1200	5.2	18	24	85	5.1	100	137.2	4.10
23	1200	4.0	34	42	62	3.0	60	135.6	4.04
24	1200	5.7	27	51	134	2.2	67	132.6	3.83
25	1200	4.8	22	21	65	4.7	64	142.6	3.9
26	1200	4.0	18	14	59	2.4	58	135.4	3.78
27	1200	5.2	23	27	74	3.1	71	139.4	3.98
28	1200	4.1	11	7	61	2.3	52	135.3	3.92
29	1200	4.4	20	15	78	2.3	59	138.3	4.02.
30	1200	4.6	17	20	130	1.3	65	138.7	3.97
31	1200	3.2	29	28	42	4.1	67	139.7	4.0
32	1200	4.2	69	47	93	3.7	77	125.2	3.21
33	1200	5.0	16	24	86	2.4	78	125.8	3.72

Continued……..

Clinical blood chemistry characteristics of 39 randomized patients at follow up visit 3 (Continued):

Subject No.	Dosage group (mg/d)	FBS mmol/L *(3.8-6.1)	SGOT U/L * (0-37)	SGPT U/L *(0-40)	ALP U/L * (39-117)	BUN mmol/L * (2.14-7.14)	CrCl umol/L * (62-124)	Na^+ mEq/L * (135-145)	K^+ mEq/L * (3.5-5)
34	1200	-	-	-	-	-	-	-	-
35	1200	4.1	14	7	61	1.7	52	127.4	3.64
36	1200	-	-	-	-	-	-	-	-
37	1200	6.1	23	49	94	5.6	107	141.4	3.91
38	1200	4.5	18	21	47	3.0	80	135.7	4.2
39	1200	6.0	19	13	74	4.9	79	137.5	4.35

*= Normal Range

Clinical blood chemistry characteristics of 39 randomized patients at follow up visit 4

Subject No.	Dosage group (mg/d)	FBS mmol/L * (3.8-6.1)	SGOT U/L * (0-37)	SGPT U/L * (0-40)	ALP U/L * (39-117)	BUN mmol/L * (2.14-7.14)	CrCl umol/L * (62-124)	Na^+ mEq/L * (135-145)	K^+ mEq/L * (3.5-5)
1	600	3.8	18	15	41	4.2	96	142.2	4.22
2	600	4.0	19	15	76	3.7	64	130.8	4.38
3	600	-	-	-	-	-	-	-	-
4	600	-	-	-	-	-	-	-	-
5	600	4.6	50	79	60	3.0	59	136.2	4.2
6	600	3.9	17	14	67	2.5	61	136.6	3.62
7	600	4.8	20	18	68	2.7	85	143	4.66
8	600	5.5	27	56	79	3.1	73	138.7	3.64
9	600	4.8	18	18	53	4.0	68	131.7	3.9
10	600	3.4	19	36	63	1.8	81	130.5	4.32
11	600	4.8	16	12	58	3.8	91	143.5	4.68
12	600	3.9	36	15	79	3.4	85	125.1	4.16
13	600	4.9	21	24	99	3.6	90	135.9	3.34
14	600	4.7	21	25	77	3.5	74	141.3	4.39
15	600	4.6	19	23	4.0	79	79	141.5	3.77
16	600	3.5	16	10	72	2.3	67	140.9	4.03

Continued.....

Clinical blood chemistry characteristics of 39 randomized patients at follow up visit 4(Continued):

Subject No.	Dosage group (mg/d)	FBS mmol/L * (3.8-6.1)	SGOT U/L * (0-37)	SGPT U/L * (0-40)	ALP U/L * (39-117)	BUN mmol/L * (2.14-7.14)	CrCl umol/L * (62-124)	Na^+ mEq/L * (135-145)	K^+ mEq/L * (3.5-5)
17	600	4.1	15	8	90	2.6	64	139.2	3.64
18	600	3.4	24	24	65	2.6	70	141.8	3.64
19	600	4.1	16	14	163	3.6	62	136	3.94
20	600	4.7	16	24	90	3.7	81	143.4	4.14
21	1200	4.5	28	44	69	2.5	85	137.8	3.1
22	1200	4.6	18	22	90	4.7	104	134.7	3.79
23	1200	4.5	26	36	62	3.2	70	135.9	4.15
24	1200	5.1	23	29	103	3.3	63	136.0	3.5
25	1200	4.7	20	20	60	6.5	59	138.6	4.01
26	1200	4.1	19	12	65	2.0	75	139.1	4.46
27	1200	5.3	28	42	73	3.3	68	143.2	4.43
28	1200	3.6	13	11	52	2.7	55	135.1	4.38
29	1200	4.3	17	10	67	1.6	61	135.8	4.17
30	1200	4.4	19	20	129	4.1	66	137.9	3.46
31	1200	3.2	29	28	42	4.1	67	139.7	4.0
32	1200	4.1	63	31	100	3.2	76	128.8	3.39

Continued .....

Clinical blood chemistry characteristics of 39 randomized patients at follow up visit 4(Continued):

Subject No.	Dosage group (mg/d)	FBS mmol/L *(3.8-6.1)	SGOT U/L * (0-37)	SGPT U/L *(0-40)	ALP U/L * (39-117)	BUN mmol/L * (2.14-7.14)	CrCl umol/L * (62-124)	Na^+ mEq/L * (135-145)	K^+ mEq/L * (3.5-5)
33	1200	5.0	19	26	88	3.2	65	128.5	4.13
34	1200	-	-	-	-	-	-	-	-
35	1200	4.5	17	8	70	1.6	61	133.4	3.1
36	1200	-	-	-	-	-	-	-	-
37	1200	5.0	31	52	110	5.6	98	139.1	3.78
38	1200	4.8	16	23	48	3.9	73	139.4	3.74
39	1200	5.0	17	12	70	4.5	75	138.1	4.25

*= Normal Range

Individual MHD plasma concentration of 39 randomized patients

MHD plasma concentrations (μg/ml)				
Patients No.	Grouping(mg/d)	Visit 3	Visit 4	average
1	600	15.35	14.41	14.88
2	600	6.33	6.49	6.41
3	600	-	-	
4	600	-	-	
5	600	8.75	6.01	7.38
6	600	5.85	5.53	5.69
7	600	8.63	9.71	9.17
8	600	3.30	3.44	3.37
9	600	5.99	7.07	6.53
10	600	5.51	5.97	5.74
11	600	7.30	5.61	6.46
12	600	8.33	8.75	8.54
13	600	7.21	6.23	6.72
14	600	4.64	-	6.64
15	600	3.61	4.37	3.99
16	600	4.67	4.65	4.66
17	600	8.18	7.85	8.02
18	600	5.44	4.20	4.82
19	600	8.20	8.09	8.20
20	600	6.73	-	6.73
21	1200	4.66	4.85	4.76
22	1200	20.43	23.96	22.20
23	1200	14.84	17.93	16.39
24	1200	10.39	10.17	10.28
25	1200	13.96	13.85	13.90
26	1200	12.64	9.38	11.01
27	1200	17.04	13.13	15.09
28	1200	19.89	17.81	18.85
29	1200	9.65	8.02	8.84
30	1200	11.96	13.34	12.65

Continued…….

Individual MHD plasma concentration (C_{min}) of 39 randomized patients

MHD plasma concentrations (μg/ml)				
Patients No.	Grouping (mg/d)	Visit 3	Visit 4	average
31	1200	7.60	7.60	7.60
32	1200	21.14	21.29	21.22
33	1200	9.12	9.08	9.10
34	1200	8.98	10.28	9.63
35	1200	-	-	-
36	1200	11.15		11.15
37	1200	6.22		6.22
38	1200	-	-	-
39	1200	12.78	12.94	12.86

วิธีทางสถิติที่ใช้ในการวิเคราะห์ผลการศึกษา

1. **A Wilcoxon Signed Ranks Test:** ใช้เพื่อเปรียบเทียบ median seizure frequency ระหว่างก่อน (baseline) และหลัง (treatment) รักษาด้วยยาออกซ์คาร์บาซีปีน ทั้งในขนาด 600 และ 1200 มก./วัน

กลุ่มผู้ป่วยที่ได้รับยาขนาด 600 มก. /วัน

No.	Baseline(X)	Treatment(Y)	IX-YI	Signed Rank of X-Y	R-
1	3.5	0.86	2.64	12	
2	8	2.57	5.43	15.5	
3	2	0	2	10	
4	58	52	6	17	
5	3	4.26	1.26	-7	-7
6	8.5	8.3	0.2	1	
7	2	1.07	0.93	3	
8	3	2.4	0.6	2	
9	2	0	2	10	
10	14	8.57	5.43	15.5	
11	5	2.3	2.7	13	
12	2.5	1.33	1.17	5	
13	4	2.95	1.05	4	
14	7	3.14	3.86	14	
15	6	8	2	-10	-10
16	10	0.57	9.43	18	
17	5	3.05	1.95	8	
18	2	0.8	1.2	6	

<u>สมมุติฐาน</u>

H_0 : ค่า median seizure frequency ระหว่างก่อนได้รับยา (baseline) และหลัง (treatment) ได้รับยา ไม่แตกต่างกัน

H_1 : ค่า median seizure frequency ระหว่างก่อนได้รับยา (baseline) และหลัง (treatment) ได้รับยา แตกต่างกัน

กำหนดระดับนัยสำคัญ (α) = 0.05

เขตปฏิเสธ

จะปฏิเสธสมมุติฐาน Ho เมื่อค่าสัมบูรณ์ที่น้อยที่สุดจากการคำนวณมีค่าน้อยกว่าหรือเท่ากับค่าวิกฤติ

ผลการทดสอบ

Rank	N	Sum of rank
Positive rank	16	154.00
Negative rank	2	**17.00**
Total	18	

ผลการทดสอบพบว่า ค่าสัมบูรณ์ที่มีค่าน้อยที่สุดอยู่ในกลุ่ม Negative rank มีค่าเท่ากับ **17.00** ซึ่งน้อยกว่า ค่าวิกฤตซึ่งมีค่าเท่ากับ **40.00** ดังนั้นจึงปฏิเสธสมมุติฐาน Ho (ค่าวิกฤติ เปิดได้จากตาราง Probability levels for the Wilcoxon Signed Rank Test)

สรุปผลการทดสอบ

การรักษาด้วยยาออกซ์คาร์บาซีปีนขนาด 600 มก. / วัน ทำให้เกิดการเปลี่ยนแปลงค่า median seizure frequency อย่างมีนัยสำคัญที่ระดับ 0.05

กลุ่มผู้ป่วยที่ได้รับยาขนาด 1200 มก. /วัน

No.	Baseline	Treatment	IX-YI	Signed Rank of X-Y	R-
1	20	3.2	16.8	17	
2	14.4	0.29	14.11	16	
3	7	5	2	6.5	
4	2	1.8	0.2	1	
5	3	8.86	5.86	-12	-12
6	3	0.86	2.14	8	
7	2	0	2	6.5	
8	4	1.7	2.3	9	
9	10	1.43	8.57	14	
10	2	0.53	1.47	5	
11	2	3	1	-3	-3
12	12	2.55	9.45	15	
13	2	1.43	0.57	2	
14	14	19.43	5.43	-11	-11
15	3	0	3	10	
16	4	2.57	1.43	4	
17	20	12.86	7.14	13	

<u>สมมุติฐาน</u>

H_0 : ค่า median seizure frequency ระหว่างก่อนได้รับยา (baseline) และหลัง (treatment) ได้รับยา ไม่แตกต่างกัน

H_1 : ค่า median seizure frequency ระหว่างก่อนได้รับยา (baseline) และหลัง (treatment) ได้รับยา แตกต่างกัน

กำหนดระดับนัยสำคัญ (α) = 0.05

เขตปฏิเสธ

จะปฏิเสธสมมุติฐาน Ho เมื่อค่าสัมบูรณ์ที่น้อยที่สุดจากการคำนวณมีค่าน้อยกว่าหรือเท่ากับค่าวิกฤติ

ผลการทดสอบ

Rank	N	Sum of rank
Positive rank	14	127.00
Negative rank	3	26.00
Total	17	

ผลการทดสอบพบว่า ค่าสัมบูรณ์ที่มีค่าน้อยที่สุดอยู่ในกลุ่ม Negative rank มีค่าเท่ากับ 26.00 ซึ่งน้อยกว่า ค่าวิกฤตซึ่งมีค่าเท่ากับ 34.00 ดังนั้นจึง **ปฏิเสธสมมุติฐาน** H_0

สรุปผลการทดสอบ

การรักษาด้วยยาออกซ์คาร์บาซีปีนขนาด 1200 มก. / วัน ทำให้เกิดการเปลี่ยนแปลงค่า median seizure frequency อย่างมีนัยสำคัญที่ระดับ 0.05

2. **A Regression Analysis** ใช้เพื่อศึกษาหาความสัมพันธ์ระหว่าง

a. Percent change (PCH) from baseline in seizure frequency กับ ตัวแปรดังนี้

a.1 weight

a.2 age

a.3 dosage

a.4 baseline seizure frequency (BSF)

a.5 sex

a.6 plasma MHD concentration

b. Plasma MHD concentration กับ dosage group

a.1 Percent change (PCH) from baseline in seizure frequency กับ ตัวแปร weight

PCH (Yi)	Weight (Xi)	X^2i	XiYi
-75.00	62.00	3844	-4650
-68.00	55.00	3025	-3740
-100.00	70.00	4900	-7000
-10.00	50.00	2500	-500
42.00	54.00	2916	2268
-2.00	65.00	4225	-130
-47.00	55.00	3025	-2585
-20.00	50.00	2500	-1000
-100.00	77.00	5929	-7700
-39.00	56.00	3136	-2184
-54.00	78.00	6084	-4212
-47.00	76.00	5776	-3572
-26.00	55.00	3025	-1430
-55.00	42.00	1764	-2310
33.00	44.00	1936	1452
-94.00	60.00	3600	-5640
-39.00	55.00	3025	-2145
-60.00	63.00	3969	-3780
-84.00	57.00	3249	-4788
-98.00	76.00	5776	-7448
-29.00	50.00	2500	-1450
-10.00	55.00	3025	-550
155.00	56.00	3136	8680
-71.00	50.00	2500	-3550
-100.00	71.00	5041	-7100
-58.00	80.00	6400	-4640
-86.00	60.00	3600	-5160
-74.00	46.00	2116	-3404
50.00	51.00	2601	2550
-79.00	80.00	6400	-6320
-28.50	60.00	3600	-1710
39.00	57.00	3249	2223
-100.00	80.00	6400	-8000
-36.00	70.00	4900	-2520
-36.00	53.00	2809	-1908

PCH (Yi)	Weight (Xi)	X^2i	XiYi
ΣY = - 1406.5	ΣX = 2119.0	ΣX^2 = 132481	ΣXY= - 93953

ก. การทดสอบความสัมพันธ์ระหว่าง PCH กับ น้ำหนัก (weight) ว่ามีความสัมพันธ์กันในรูปเชิงเส้นหรือไม่

<u>สมมุติฐาน</u>

Ho : $\beta 1 = 0$; PCH กับ น้ำหนัก (weight) ไม่มีความสัมพันธ์กันในลักษณะเชิงเส้น

H1 : $\beta 1 \neq 0$; PCH กับ น้ำหนัก (weight) มีความสัมพันธ์กันในลักษณะเชิงเส้น

กำหนดระดับนัยสำคัญ (α) = 0.05

<u>สถิติทดสอบ</u>

$$t = b / (S/ \sqrt{SSxx})$$

เนื่องจาก $SSxx = \Sigma x^2 - (\Sigma x)^2 / N = 132481 - (2119)^2/35 = 4191$

$SSxy = \Sigma xy - (\Sigma X)(\Sigma Y)/N = (-93953) - (2119)(-1406.5)/35$

$= (-) 8799$

ดังนั้น $b = SSxy / SSxx = (-) 8799 / 4191 = (-) 2.10$

เนื่องจาก $SSyy = \Sigma Y^2 - (\Sigma Y)^2/n$

$= 156688 - (-1406.5)^2 / 35 = 156688-56521 = 100167$

ดังนั้น $S^2 = \frac{SSyy - b\ SSxy}{n-2} = \frac{100167- (-2.10)(-8799)}{35-2} = 2475$

ดังนั้น $S = 49.75$

<u>แทนค่า</u> $t = -2.10 / 49.75/ 64.74 = (-) 2.73$

<u>เขตปฏิเสธ</u> : จะปฏิเสธสมมุติฐาน Ho ถ้า $|t| > t_{1-\alpha/2;\, n-2}$

หรือ กล่าวได้ว่า จะปฏิเสธ ถ้า $|t| > t_{.975;\, 33}$ โดยที่ $t_{.975;\, 33} = 2.0345$

แต่ $|t| = 2.73$ ซึ่ง > 2.0345

จึงปฏิเสธสมมุติฐาน Ho นั่นคือ PCH กับ น้ำหนัก (weight) มีความสัมพันธ์กันในลักษณะเชิงเส้น ที่ระดับนัยสำคัญ (α) = 0.05

ข. เมื่อ PCH มีความสัมพันธ์ในรูปเชิงเส้น กับ น้ำหนัก (weight) จะมีสมการความถดถอย คือ $Y_i = \beta_0 + \beta_1 X_i + e_i$

ซึ่งประมาณได้ด้วยสมการแสดงความสัมพันธ์ดังนี้

$$\hat{Y}_i = a + b X_i \; ; \; i = 1,2,\ldots,35$$

ซึ่งจะสามารถคำนวณหาค่า a และ b ได้ดังนี้

$$SSxx = \sum x^2 - \frac{(\sum x)^2}{N} = 132481 - \frac{(2119)^2}{35} = 132481 - 128290 = 4191$$

$$SSxy = \sum xy - \frac{(\sum X)(\sum Y)}{N} = (-93953) - \frac{(2119)(-1406.5)}{35} = (-93953) + 85154$$

$$= -8799$$

ดังนั้น $b = SSxy / SSxx = -8799 / 4191 = (-)\ 2.10$

$a = \bar{y} - (b)(\bar{x}) = (-1406.5)/35 - (-2.10)(2119/35)$

$= (-40.2) + (2.10)(60.54) = 86.94$

ดังนั้น สมการแสดงความสัมพันธ์ PCH และ น้ำหนัก (weight) คือ

$$\hat{y}_i = 86.94 - 2.1\, X_i$$

<u>สรุปผลการทดสอบ</u>

จากผลการทดสอบ ในข้อ ก. และ ข.สามารถสรุปได้ว่า PCH และ น้ำหนัก (weight) มีความสัมพันธ์กันในรูปเชิงเส้นที่ระดับนัยสำคัญ 0.05 โดยที่สมการซึ่งแสดงความสัมพันธ์เป็น $\hat{y}_i = 86.94 - 2.1\, X_i$

a.2 Percent change (PCH) from baseline in seizure frequency **กับ ตัวแปร** age

ก. ทดสอบความสัมพันธ์ระหว่าง PCH กับ age ว่ามีความสัมพันธ์กันในรูปเชิงเส้นหรือไม่

<u>สมมุติฐาน</u>

Ho : $\beta 1 = 0$; PCH กับ age ไม่มีความสัมพันธ์กันในรูปเชิงเส้น

H1 : $\beta 1 \neq 0$; PCH กับ age มีความสัมพันธ์กันในรูปเชิงเส้น

กำหนดระดับนัยสำคัญ (α) = 0.05

PCH (Yi)	Y^2i	Age (Xi)	X^2i	XiYi
-75	5625	26	676	-1950
-68	4624	26	676	-1768
-100	10000	36	1296	-3600
-10	100	36	1296	-360
42	1764	37	1369	1554
-2	4	18	324	-36
-47	2209	28	784	-1316
-20	400	24	576	-480
-100	10000	44	1936	-4400
-39	1521	39	1521	-1521
-54	2916	37	1369	-1998
-47	2209	36	1296	-1692
-26	676	33	1089	-858
-55	3025	35	1225	-1925
33	1089	19	361	627
-94	8836	25	625	-2350
-39	1521	20	400	-780
-60	3600	25	625	-1500
-84	7056	25	625	-2100
-98	9604	41	1681	-4018
-29	841	43	1849	-1247
-10	100	38	1444	-380

PCH (Yi)	Y^2i	Age (Xi)	X^2i	XiYi
155	24025	29	841	4495
-71	5041	36	1296	-2556
-100	10000	25	625	-2500
-58	3364	33	1089	-1914
-86	7396	28	784	-2408
-74	5476	26	676	-1924
50	2500	27	729	1350
-79	6241	39	1521	-3081
-28.5	812.25	36	1296	-1026
39	1521	35	1225	1365
-100	10000	32	1024	-3200
-36	1296	37	1369	-1332
-36	1296	44	1936	-1584
ΣY= -1406.5	Σ^2=156688	ΣX=1118	ΣX^2=37454	ΣXY=-46413

<u>สถิติทดสอบ</u>

$$t = b / (S/\sqrt{SSxx})$$

เนื่องจาก $SSxx = \Sigma x^2 - \frac{(\Sigma x)^2}{N} = 37454 - (1118)^2/35 = 1742$

$SSxy = \Sigma xy - (\Sigma X)(\Sigma Y)/N = (-46413) - (1118)(-1406.5)/35$

$= (-) 1485$

ดังนั้น $b = SSxy / SSxx = (-) 1485 / 1742 = (-) 0.85$

เนื่องจาก $SSyy = \Sigma Y^2 - (\Sigma Y)^2/n$

$= 156688 - (-1406.5)^2 / 35 = 156688-56521 = 100167$

ดังนั้น $S^2 = \frac{SSyy - b\,SSxy}{n-2} = \frac{100167- (-0.85)(-1485)}{35-2} = 2997$

ดังนั้น $S = 54.74$

แทนค่า $t = (-) 0.85 / 54.74 / 41.74 = (-) 0.65$

เขตปฏิเสธ : จะปฏิเสธสมมุติฐาน Ho ถ้า $|t| > t_{1-\alpha/2;n-2}$

หรือ กล่าวได้ว่า จะปฏิเสธ ถ้า $|t| > t_{.975;33}$ โดยที่ $t_{.975;33} = 2.0345$

แต่ $|t| = 0.65$ ซึ่ง < 2.0345 จึงยอมรับสมมุติฐาน Ho

สรุปผลการทดสอบ

PCH กับ ageไม่มีความสัมพันธ์กันในรูปเชิงเส้น ที่ระดับนัยสำคัญ (α) = 0.05

a.3 Percent change (PCH) from baseline in seizure frequency **กับ ตัวแปร** dosage

ก. ทดสอบความสัมพันธ์ระหว่าง PCH กับ dosage ว่ามีความสัมพันธ์กันในรูปเชิงเส้นหรือไม่

<u>สมมุติฐาน</u>

Ho : $\beta 1 = 0$; PCH กับ dosage ไม่มีความสัมพันธ์กันในรูปเชิงเส้น

H1 : $\beta 1 \neq 0$; PCH กับ dosage มีความสัมพันธ์กันในรูปเชิงเส้น

กำหนดระดับนัยสำคัญ (α) = 0.05

PCH (Yi)	Y^2i	Dose* (Xi)	X^2i	XiYi
-75	5625	1	1	-75
-68	4624	1	1	-68
-100	10000	1	1	-100
-10	100	1	1	-10
42	1764	1	1	42
-2	4	1	1	-2
-47	2209	1	1	-47
-20	400	1	1	-20
-100	10000	1	1	-100
-39	1521	1	1	-39
-54	2916	1	1	-54
-47	2209	1	1	-47
-26	676	1	1	-26
-55	3025	1	1	-55
33	1089	1	1	33
-94	8836	1	1	-94
-39	1521	1	1	-39
-60	3600	1	1	-60

PCH (Yi)	Y^2i	Dose*(Xi)	X^2i	XiYi
-98	9604	2	4	-196
-29	841	2	4	-58
-10	100	2	4	-20
155	24025	2	4	310
-71	5041	2	4	-142
-100	10000	2	4	-200
-58	3364	2	4	-116
-86	7396	2	4	-172
-74	5476	2	4	-148
50	2500	2	4	100
-79	6241	2	4	-158
-28.5	812.25	2	4	-57
39	1521	2	4	78
-100	10000	2	4	-200
-36	1296	2	4	-72
-36	1296	2	4	-72
ΣY= -1406.5	ΣY^2=156688	ΣX=52	ΣX^2=86	ΣXY=-2052

* 1 = 600 mg/d, 2 = 1200 mg/d

<u>สถิติทดสอบ</u>

$$t = b / (S/ \sqrt{SSxx})$$

เนื่องจาก $SSxx = \Sigma x^2 - (\Sigma x)^2 / N = 86 - (52)^2/35 = 8.74$

$SSxy = \Sigma xy - (\Sigma X)(\Sigma Y)/N = (-2052) - (52)(-1406.5)/35$

$= 38$

ดังนั้น $b = SSxy / SSxx = 38 / 8.74 = 4.35$

เนื่องจาก $SSyy = \sum Y^2 - (\sum Y)^2/n$

$= 156688 - (-1406.5)^2 / 35 = 156688-56521 = 100167$

ดังนั้น $S^2 = \frac{SSyy - b\ SSxy}{n-2} = \frac{100167- (4.35)(38)}{35-2} = 3030$

ดังนั้น $S = 55$

<u>แทนค่า</u> $t = 4.35 / 55/ 3 = 0.24$

<u>เขตปฏิเสธ</u> :

จะปฏิเสธสมมุติฐาน Ho ถ้า $|t| > t_{1-\alpha/2;\ n-2}$

หรือ กล่าวได้ว่า จะปฏิเสธ ถ้า $|t| > t_{.975;\ 33}$ โดยที่ $t_{.975;\ 33} = 2.0345$

แต่ $|t| = 0.24$ ซึ่ง < 2.0345 จึงยอมรับสมมุติฐาน Ho

<u>สรุปผลการทดสอบ</u>

PCH กับ dosageไม่มีความสัมพันธ์กันในรูปเชิงเส้น ที่ระดับนัยสำคัญ (α) = 0.05

a.4 Percent change (PCH) from baseline in seizure frequency **กับ ตัวแปร** baseline seizure frequency(BSF)

ก. ทดสอบความสัมพันธ์ระหว่าง PCH กับ BSFว่ามีความสัมพันธ์กันในรูปเชิงเส้นหรือไม่

<u>สมมุติฐาน</u>

Ho : $\beta 1 = 0$; PCH กับ BSF ไม่มีความสัมพันธ์กันในรูปเชิงเส้น

H1 : $\beta 1 \neq 0$; PCH กับ BSF มีความสัมพันธ์กันในรูปเชิงเส้น

กำหนดระดับนัยสำคัญ (α) = 0.05

PCH (Yi)	Y^2i	BSF (Xi)	X^2i	XiYi
-75	5625	4	16	-300
-68	4624	8	64	-544
-100	10000	2	4	-200
-10	100	58	3364	-580
42	1764	3	9	126
-2	4	9	81	-18
-47	2209	2	4	-94
-20	400	3	9	-60
-100	10000	2	4	-200
-39	1521	14	196	-546
-54	2916	5	25	-270
-47	2209	3	9	-141
-26	676	4	16	-104
-55	3025	7	49	-385
33	1089	6	36	198
-94	8836	10	100	-940
-39	1521	5	25	-195
-60	3600	2	4	-120
-84	7056	20	400	-1680
-98	9604	14	196	-1372

PCH (Yi)	Y^2i	BSF (Xi)	X^2i	XiYi
-29	841	7	49	-203
-10	100	2	4	-20
155	24025	3	9	465
-71	5041	3	9	-213
-100	10000	2	4	-200
-58	3364	4	16	-232
-86	7396	10	100	-860
-74	5476	2	4	-148
50	2500	2	4	100
-79	6241	12	144	-948
-28.5	812.25	2	4	-57
39	1521	14	196	546
-100	10000	3	9	-300
-36	1296	4	16	-144
-36	1296	20	400	-720
ΣY= -1406.5	ΣY^2=156688	ΣX=271	ΣX^2=5579	$\Sigma X Y$=-10359

<u>สถิติทดสอบ</u>

$$t = b / (S/ \sqrt{SSxx})$$

เนื่องจาก $SSxx = \Sigma x^2 - (\Sigma x)^2 / N = 5579 - (271)^2/35 = 34$

$SSxy = \Sigma xy - (\Sigma X)(\Sigma Y)/N = (-10359) - (271)(-1406.5) /35$

$= 531$

ดังนั้น $b = SSxy / SSxx = 531 / 3481 = 0.15$

เนื่องจาก $SSyy = \sum Y^2 - (\sum Y)^2/n$

$= 156688 - (-1406.5)^2 / 35 = 156688\text{-}56521 = 100167$

ดังนั้น $S^2 = \frac{SSyy - b\ SSxy}{n-2} = \frac{100167 - (0.15)(531)}{35-2} = 3033$

ดังนั้น $S = 55$

<u>แทนค่า</u> $t = 0.15 / (55/59) = 0.16$

<u>เขตปฏิเสธ</u> :

จะปฏิเสธสมมุติฐาน Ho ถ้า $|t| > t_{1-\alpha/2;\ n-2}$

หรือ กล่าวได้ว่า จะปฏิเสธ ถ้า $|t| > t_{.975;\ 33}$ โดยที่ $t_{.975;\ 33} = 2.0345$

แต่ $|t| = 0.16$ ซึ่ง < 2.0345 จึงยอมรับสมมุติฐาน Ho

<u>สรุปผลการทดสอบ</u>

PCH กับ BSF ไม่มีความสัมพันธ์กันในรูปเชิงเส้น ที่ระดับนัยสำคัญ (α) = 0.05

a.5 Percent change (PCH) from baseline in seizure frequency **กับ ตัวแปร** sex

ก. ทดสอบความสัมพันธ์ระหว่าง PCH กับ sex ว่ามีความสัมพันธ์กันในรูปเชิงเส้นหรือไม่

<u>สมมุติฐาน</u>

Ho : $\beta 1 = 0$; PCH กับ sex ไม่มีความสัมพันธ์กันในรูปเชิงเส้น

H1 : $\beta 1 \neq 0$; PCH กับ sex มีความสัมพันธ์กันในรูปเชิงเส้น

กำหนดระดับนัยสำคัญ (α) = 0.05

PCH (Yi)	Y^2i	Sex* (Xi)	X^2i	XiYi
-75	5625	0	0	0
-68	4624	0	0	0
-100	10000	1	1	-100
-10	100	1	1	-10
42	1764	0	0	0
-2	4	1	1	-2
-47	2209	1	1	-47
-20	400	0	0	0
-100	10000	0	0	0
-39	1521	1	1	-39
-54	2916	0	0	0
-47	2209	0	0	0
-26	676	0	0	0
-55	3025	1	1	-55
33	1089	0	0	0
-94	8836	0	0	0
-39	1521	1	1	-39
-60	3600	0	0	0
-84	7056	0	0	0
-98	9604	0	0	0
-29	841	1	1	-29
-10	100	0	0	0

PCH (Yi)	Y^2i	Sex* (Xi)	X^2i	XiYi
155	24025	1	1	155
-71	5041	1	1	-71
-100	10000	0	0	0
-58	3364	1	1	-58
-86	7396	1	1	-86
-74	5476	1	1	-74
50	2500	1	1	50
-79	6241	0	0	0
-28.5	812.25	0	0	0
39	1521	1	1	39
-100	10000	0	0	0
-36	1296	1	1	-36
-36	1296	1	1	-36
ΣY= -1406.5	ΣY^2=156688	ΣX=17	ΣX^2=17	$\Sigma X Y$=-438

* 0 = male, 1 = female

<u>สถิติทดสอบ</u>

$$t = b / (S/\sqrt{SSxx})$$

เนื่องจาก $SSxx = \Sigma x^2 - (\Sigma x)^2 / N = 17 - (17)^2/35 = 8.26$

$$SSxy = \Sigma xy - (\Sigma X)(\Sigma Y)/N = (-438) - (17)(-1406.5)/35 = 245$$

ดังนั้น $b = SSxy / SSxx = 245 / 8.26 = 30$

เนื่องจาก $SSyy = \Sigma Y^2 - (\Sigma Y)^2/n$

$= 156688 - (-1406.5)^2 / 35 = 156688-56521 = 100167$

ดังนั้น S^2 = $\frac{SSyy - b\ SSxy}{n-2}$ = $\frac{100167 - (30)(245)}{35-2}$ = 2813

ดังนั้น S = 53

แทนค่า t = 30 / (53/2.87)= 1.62

เขตปฏิเสธ : จะปฏิเสธสมมุติฐาน Ho ถ้า $|t| > t_{1-\alpha/2;\ n-2}$

หรือ กล่าวได้ว่า จะปฏิเสธ ถ้า $|t| > t_{.975;\ 33}$ โดยที่ $t_{.975;\ 33} = 2.0345$

แต่ $|t| = 1.62$ ซึ่ง < 2.0345 จึงยอมรับสมมุติฐาน Ho

สรุปผลการทดสอบ

PCH กับ BSF ไม่มีความสัมพันธ์กันในรูปเชิงเส้น ที่ระดับนัยสำคัญ (α) = 0.05

a.6 Percent change (PCH) from baseline in seizure frequency **กับ ตัวแปร** plasma MHD concentration

ก. ทดสอบความสัมพันธ์ระหว่าง PCH กับ plasma MHD concentration ว่ามีความสัมพันธ์กันในรูปเชิงเส้นหรือไม่

<u>สมมุติฐาน</u>

Ho : $\beta 1 = 0$; PCH กับ plasma MHD concentration ไม่มีความสัมพันธ์กันในรูปเชิงเส้น

H1 : $\beta 1 \neq 0$; PCH กับ plasma MHD concentration มีความสัมพันธ์กันในรูปเชิงเส้น

กำหนดระดับนัยสำคัญ (α) = 0.05

PCH Yi	Plasma MHD concentration Xi	$X^2 i$	XiYi
-75.00	14.88	221.41	-1116
-68.00	6.41	41	-435.9
-100.00	7.38	54.5	-738
-10.00	5.69	32.4	-56.9
42.00	9.17	84.1	385.14
-2.00	3.37	11.36	-6.74
-47.00	6.53	42.6	-306.91
-20.00	5.74	32.9	-114.8
-100.00	6.46	41.7	-646
-39.00	8.54	72.9	-333.06
-54.00	6.72	45.2	-362.88
-47.00	4.64	21.5	-218.08
-26.00	3.99	15.9	-103.74
-55.00	4.66	21.7	-256.3
33.00	8.02	64.3	264.66
-94.00	4.82	23.2	-453.08
-39.00	8.20	67.2	-319.8
-60.00	6.73	45.3	-403.8
-84.00	4.76	22.7	-399.84
-98.00	22.20	492.8	-2175.6
-29.00	16.39	268.6	-475.31
-10.00	10.28	105.7	-102.8
155.00	13.90	193.2	2154.5
-71.00	11.01	121.2	-781.71

PCH Yi	Plasma MHD concentration Xi	$X^2 i$	XiYi
-100.00	15.09	227.7	-1509
-58.00	18.85	355.3	-1093.3
-86.00	8.84	78.2	-760.24
-74.00	12.65	160	-936.1
50.00	7.60	57.8	380
-79.00	21.22	450.3	-1676.38
-28.50	9.10	82.8	-259.35
39.00	9.63	92.7	-375.57
-100.00	11.15	124.3	1115
-36.00	6.22	38.7	-223.92
-36.00	12.86	165.4	-462.96
$\Sigma Y = -1406.5$	$\Sigma X = 333.7$	$\Sigma X^2 = 3976.87$	$\Sigma XY = -14283.6$

<u>สถิติทดสอบ</u>

$$t = b / (S/ \sqrt{SSxx})$$

เนื่องจาก $SSxx = \Sigma x^2 - \frac{(\Sigma x)^2}{N} = 3976.87 - \frac{(333.7)^2}{35}$

$= 795.27$

$SSxy = \Sigma xy - \frac{(\Sigma X)(\Sigma Y)}{N} = (-14283.6) - \frac{(333.7)(-1406.5)}{35}$

$= (-14283.6) + 13410$

$= - 873.6$

ดังนั้น $b = SSxy / SSxx = - 873.6/795.27 = - 1.1$

เนื่องจาก $SSyy = \Sigma Y^2 - (\Sigma Y)^2/n$

$= 156688 - (-1406.5)^2 / 35 = 156688-56521 = 100167$

ดังนั้น $S^2 = \frac{SSyy - b\ SSxy}{n-2} = \frac{100167- (-1.1)(-873.6)}{35-2} = \frac{100167-961}{33}$

$= 30279$

ดังนั้น S = 174

<u>แทนค่า</u> t = -1.1 / (174/ 28.2) = - 0.178

<u>เขตปฏิเสธ</u> :

จะปฏิเสธสมมุติฐาน Ho ถ้า $|t| > t_{1-\alpha/2;\, n-2}$

หรือ กล่าวได้ว่า จะปฏิเสธ ถ้า $|t| > t_{.975;\, 33}$ โดยที่ $t_{.975;\, 33} = 2.0345$

แต่ $|t| = 0.178$ ซึ่ง < 2.0345

จึงยอมรับสมมุติฐาน Ho

<u>สรุปผลการทดสอบ</u>

PCH ไม่มีความสัมพันธ์กับ plasma MHD concentration ในรูปเชิงเส้น ที่ระดับนัยสำคัญ 0.05

b. Plasma MHD concentration กับ dosage group

ก. ทดสอบความสัมพันธ์ระหว่าง Plasma MHD concentration กับ dosage group ว่าอยู่ในรูปเชิงเส้นหรือไม่

<u>สมมุติฐาน</u>

Ho : $\beta 1 = 0$; plasma MHD concentration กับ dosage group ไม่มีความสัมพันธ์กันในรูปเชิงเส้น

H1 : $\beta 1 \neq 0$; plasma MHD concentration กับ dosage group มีความสัมพันธ์กันในรูปเชิงเส้น

กำหนดระดับนัยสำคัญ (α) = 0.05

Plasma MHD concentration Yi	Dosage group* Xi	X^2i	Y^2i	$XiYi$
14.88	1	1	221.41	14.88
6.41	1	1	41	6.41
7.38	1	1	54.5	7.38
5.69	1	1	32.4	5.69
9.17	1	1	84.1	9.17
3.37	1	1	11.36	3.37
6.53	1	1	42.6	6.53
5.74	1	1	32.9	5.74
6.46	1	1	41.7	6.46
8.54	1	1	72.9	8.54
6.72	1	1	45.2	6.72
4.64	1	1	21.5	4.64
3.99	1	1	15.9	3.99
4.66	1	1	21.7	4.66
8.02	1	1	64.3	8.02
4.82	1	1	23.2	4.82
8.20	1	1	67.2	8.20
6.73	1	1	45.3	6.73
4.76	2	4	22.7	9.52
22.20	2	4	492.8	44.4
16.39	2	4	268.6	32.78
10.28	2	4	105.7	20.56

Plasma MHD concentration	Dosage group*	X^2i	Y^2i	XiYi
Yi	Xi	4	193.2	27.8
13.90	2	4	121.2	22.02
11.01	2	4	227.7	30.18
15.09	2	4	355.3	37.7
18.85	2	4	78.2	17.68
8.84	2	4	160	25.3
12.65	2	4	57.8	15.2
7.60	2	4	450.3	42.44
21.22	2	4	82.8	18.2
9.10	2	4	92.7	19.26
9.63	2	4	124.3	22.3
11.15	2	4	38.7	12.44
6.22	2	4	165.4	25.72
12.86	2			
ΣY =333.7	ΣX = 52	ΣX^2 = 86	ΣY^2 = 3976.87	ΣXY= 545.45

*1 = 600 mg/d dosage, 2 = 1200 mg/d dosage

<u>สถิติทดสอบ</u>

$$t = b / (S/\sqrt{SSxx})$$

เนื่องจาก $SSxx = \Sigma x^2 - (\Sigma x)^2/n = 86 - (52)^2/35$

$= 8.74$

$SSxy = \Sigma xy - (\Sigma X)(\Sigma Y)/n = 545.45 - (52*333.7)/35$

$= 49.67$

ดังนั้น $b = SSxy / SSxx = 49.67/8.74 = 5.68$

เนื่องจาก $SSyy = \Sigma Y^2 - (\Sigma Y)^2/n = 3976.87 - (333.7)^2 / 35 = 795.28$

ดังนั้น $S^2 = \frac{SSyy - b\,SSxy}{n-2} = \frac{795.28 - (5.68)(49.67)}{35-2} = 15.55$

ดังนั้น $S = 3.94$

แทนค่า t = 5.68 / (3.94/ 2.96) = 5.68/1.33 = **4.27**

เขตปฏิเสธ :

จะปฏิเสธสมมุติฐาน Ho ถ้า I t I > $t_{1-\alpha/2;\ n-2}$

หรือ กล่าวได้ว่า จะปฏิเสธ ถ้า I t I > $t_{.975;\ 33}$ โดยที่ $t_{.975;\ 33}$ = 2.0345

ซึ่งจากการทดสอบ I t I = 4.27 ซึ่ง> 2.0345 จึงปฏิเสธสมมุติฐาน Ho

ผลการทดสอบ

Plasma MHD concentration กับ dosage group มีความสัมพันธ์กันในรูปเชิงเส้น

ข. เมื่อ Plasma MHD concentration กับ dosage group มีความสัมพันธ์กันในรูปเส้นตรงจะมีสมการความถดถอย คือ $Y_i = \beta_0 + \beta_1 X_i + e_i$

ซึ่งประมาณได้ด้วยสมการแสดงความสัมพันธ์ดังนี้

$$\hat{Y}_i = a + b X_i \ ; \ i = 1,2,\ldots,35$$

คำนวณหาค่า a และ b ดังนี้

$SS_{xx} = \sum x^2 - \frac{(\sum x)^2}{N}$ = 8.74

$SS_{xy} = \sum xy - \frac{(\sum X)(\sum Y)}{N}$ = 49.67

ดังนั้น $b = SS_{xy} / SS_{xx}$ = **5.68**

$a = \bar{y} - (b)(\bar{x})$ = 9.53 – 5.68(1.49)

= **1.07**

ดังนั้น สมการแสดงความสัมพันธ์ระหว่าง Plasma MHD concentration กับ dosage group คือ

$$\hat{y}_i = 1.07 + 5.68\ X_i$$

<u>สรุปผลการทดสอบ</u>

จากผลการทดสอบ ในข้อ ก. และ ข. สามารถสรุปได้ว่า Plasma MHD concentration กับ dosage group มีความสัมพันธ์กันในรูปเชิงเส้นที่ระดับนัยสำคัญ 0.05 โดยที่สมการซึ่งแสดงความสัมพันธ์เป็น $\hat{y}_i = 1.07 + 5.68 X_i$

3. **A Wilcoxon Ranks Sum Test;** ใช้เพื่อเปรียบเทียบ ค่า median PCH ระหว่างกลุ่มที่ได้รับยาขนาด 600 และ 1200 มก./วัน

<u>สมมุติฐาน</u>

Ho : ค่า median PCH ระหว่าง กลุ่มที่ได้รับยาขนาด 600 และ 1200 มก./ วันไม่แตกต่างกัน

H1 : ค่า median PCH ระหว่าง กลุ่มที่ได้รับยาขนาด 600 และ 1200 มก./ วันแตกต่างกัน

กำหนดระดับนัยสำคัญ α = 0.05

600 mg/d group		1200 mg/d group	
Rank	%PCH	Rank	%PCH
10	↓75%	8	↓84%
13	↓68%	5	↓98%
2.5	↓100%	25	↓29%
28	↓10%	29	↓10%
33	↑42%	35	↑155%
30	↓2%	12	↓71%
18.5	↓47%	2.5	↓100%
27	↓20%	15	↓58%
2.5	↓100%	7	↓86%
20.5	↓39%	11	↓74%
17	↓54%	34	↑50%
18.5	↓47%	9	↓79%
26	↓26%	24	↓28.5%
16	↓55%	32	↑39%
31	↑33%	2.5	↓100%
6	↓94%	22.5	↓36%
20.5	↓39%	22.5	↓36%
14	↓60%		
S2 = 334.5 (n=18)		S1 = 295.5 (n=17)	

สถิติทดสอบ

$$T' = n_1 (n_1+n_2+1) - T$$

เมื่อ T คือผลรวมของอันดับ (rank) ของข้อมูลในกลุ่มประชากรที่มีผลรวมของอันดับน้อยกว่า

n_1 คือจำนวนประชากรที่มีผลรวมของอันดับน้อยกว่า

n_2 คือจำนวนประชากรที่มีผลรวมของอันดับมากกว่า

เขตปฏิเสธ

ถ้า $T < T'$;

จะพิจารณาปฏิเสธ Ho เมื่อ $T < U_{\alpha(0.05)}$ (U_α = critical limit ซึ่งได้มาจากการเปิดตาราง)

ถ้า $T > T'$;

จะพิจารณาปฏิเสธ Ho เมื่อ $T' < U_{\alpha(0.05)}$

แทนค่า

$$T' = n_1 (n_1+n_2+1) - T$$

$T' = 17 (17+18+1) /295.5 = 316.5$

ดังนั้น $T < T'$

เมื่อเปิดตารางค่าวิกฤต; n_1 =17, n_2 =18, $U_{0.05}$มีค่าเท่ากับ 246

ผลการทดสอบ

ค่า T ที่คำนวณได้ คือ 295.5 ซึ่งมีค่ามากกว่าค่าวิกฤต 246 ดังนั้น จึงยอมรับ Ho (ค่าวิกฤตเปิดได้จากตารางCritical Values of ΣRx for the Mann-Whitney (Wilcoxon) Rank-Sum Test)

สรุปผลการทดสอบ

ค่า median PCH ระหว่าง กลุ่มที่ได้รับยาขนาด 600 และ 1200 มก./ วัน ไม่แตกต่างกันที่ระดับนัยสำคัญ 0.05

VITA

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