# CHAPTER II

# REVIEW OF LITERATURES

## EPILEPSY

It is one of the most common chronic neurological disorders worldwide. Approximately 2 million persons in the United States of America (USA) have epilepsy. In addition, 3% of persons in general population will have epilepsy at some point in their lives (World Health Organization (WHO), 1998). A seizure is a sudden stereotyped episode with change in motor activity, sensation, behavior, emotion, memory or consciousness due to an abnormal electrical discharge in the brain. Epilepsy is a condition of recurrent spontaneous seizures. Hence, seizure is an event and epilepsy is a disorder.

The term "epilepsy" encompasses a number of different syndromes whose cardinal feature is a predisposition to recurrent unprovoked seizures. Epilepsy syndromes can be classified according to the type of seizure, the presence or absence of neurological or development abnormalities, and electroencephalographic (EEG) findings.

Epilepsy syndromes fall into two broad categories: generalized and partial (or localization-related) syndromes. In generalized epilepsies, the predominant type of seizure begins simultaneously in both cerebral hemispheres. In partial epilepsies, by contrast, seizures originate in one or more localized foci, although they can spread to involve the entire brain (Chang and Lowenstein, 2003).

The method of classification which is now most widely used is devised by the International League Against Epilepsy (ILAE), classified by using six criteria: clinical form; interictal EEG; ictal EEG; anatomical substrate; age; and etiology. The latest revision was proposed in 1981, and officially adopted in 1982 (Commission on Classification and Terminology of the International League Against Epilepsy, 1985: 268-278, 1989: 389-399). (Table 1)

**Table 1** The International League Against Epilepsy (ILAE) classification of seizure type (Commission on Classification and Terminology of the International League Against Epilepsy, 1985: 268-278, 1989: 389-399).

**1. Partial Seizures (Focal, start in one place)**

*A. Simple partial seizures (no loss of consciousness/memory)*

1. With somatosensory or special sensory symptoms: somatosensory, visual, auditory, olfactory, gustatory, vertiginous, simple hallucination

2. With motor signs: focal motor with or without march, versive, postural, phonatory

3. With psychic symptoms: dysphasic, dysmnestic, cognitive, affective, illusions, structural hallucinations

4. With autonomic symptoms or signs, including epigastric aura

*B. Complex partial seizures (loss of consciousness/memory)*

1. Simple partial onset followed by impairment of consciousness

With simple partial features (A1 to A4) followed by impaired consciousness

With automatisms

2. With impairment of consciousness at onset

With impairment of consciousness only

With automatisms

*C. Partial seizures evolving to secondarily generalized seizures*

1. Simple partial seizure evolving to generalized seizures

2. Complex partial seizures evolving to generalized seizures

3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

**Table 1** The International League Against Epilepsy (ILAE) classification of seizure type (continued)

| |
|---|
| **2. Generalized** |
| *A. Absence, typical or atypical (petit mal)* |
| 1. Absence seizures with impairment of consciousness only, mild clonic components, atonic components, tonic component, automatisms, autonomic components |
| 2. Atypical absence seizures with changes in tone more pronounced than in A1 and with onset and/or cessation that is not abrupt |
| *B. Myoclonic seizures* |
| *C. Clonic* |
| *D. Tonic seizures* |
| *E. Tonic-clonic seizure* |
| *F. Atonic seizures* (Combinations may occurs, such as B and F or B and D) |
| **3. Unclassified epileptic seizures** |

There are many causes of seizure. For instance, genetically defects, head injury, brain tumors, infections, dysplasia, stroke, chemical imbalance or abnormality of hormones. However, more than half of cases cause of seizures cannot be identified.

Provocation of epilepsy may occurs by various triggers. Common triggers of epilepsy are stress condition, lack of sleep, hyperventilation state, and migraine (Fisher and Saul, 2003)

## EPILEPSY THERAPY

Although there are many antiepileptic drugs (AEDs), but it can be categorized by mechanisms of action into 3 categories: voltage-gated sodium channels blockade, an effect which is brought about via prolongation of the recovery phase of the channels after their activation. Indirect or direct enhancement of GABAergic neurotransmission, and inhibition of excitatory glutamatergic neurotransmission. (Table 2)

**Table 2** Common mechanisms of antiepileptic drugs

(Brodie and Kwan, 2002)

| *Drug* | *$Na^+$ channels* | *$Ca^{++}$ channels* | *$K^+$ channels* | *Inhibitory transmission* | *Excitatory transmission* |
|---|---|---|---|---|---|
| **Phenytoin** | +++ | + | | | |
| **Carbamazepine** | +++ | | | | |
| **Sodium valproate** | + | + | | ++ | + |
| **Ethosuximide** | | +++ | | | |
| **Phenobarbital** | | + | | +++ | + |
| **Benzodiazepines** | | | | +++ | |
| **Lamotrigine** | +++ | + | | | |
| **Oxcarbazepine** | +++ | + | + | | |
| **Zonisamide** | ++ | ++ | | | |
| **Vigabatrin** | | | | +++ | |
| **Tiagabine** | | | | +++ | |
| **Gabapentin** | + | + | | ++ | |
| **Felbamate** | ++ | + | | ++ | ++ |
| **Topiramate** | ++ | ++ | | ++ | ++ |
| **Levetiracetam** | | + | + | + | + |

+++ = primary action; ++ = probable action; + = possible action.

By spectrum of effectiveness, AEDs can be classified into 2 categories; broad-spectrum AEDs, AEDs which are effective against on most of seizure types, example of AEDs of this group are valproic acid, topiramate, levetiracetam, and zonisamide. Restricted-spectrum AEDs, AEDs which effective on some types of seizure, example of AEDs of this group are phenytoin, vigabatrin, gabapentin, tiagabine, and Oxcarbazepine (Table 3).

**Table 3** Efficacy of antiepileptic drugs for common seizure types (Brodie and Kwan, 2002)

| *Drug* | *Partial* | *Tonic-clonic* | *Absence* | *Myoclonic* | *Atonic/tonic* |
|---|---|---|---|---|---|
| **Phenobarbital** | + | + | **0** | ?+ | ? |
| **Phenytoin** | + | + | - | - | **0** |
| **Carbamazepine** | + | + | - | - | **0** |
| **Sodium valproate** | + | + | + | + | + |
| **Ethosuximide** | **0** | **0** | + | **0** | **0** |
| **Benzodiazepines** | + | + | ? | + | + |
| **Gabapentin** | + | + | - | - | **0** |
| **Lamotrigine** | + | + | + | + | + |
| **Oxcarbazepine** | + | + | **0** | **0** | **0** |
| **Topiramate** | + | + | ? | + | + |
| **Tiagabine** | + | + | - | - | **0** |
| **Zonisamide** | + | + | ?- | + | ?+ |
| **Levetiracetam** | + | + | + | + | ? |
| **Felbamate** | + | + | ?+ | ?+ | + |
| **Vigabatrin** | + | + | - | - | ? |

+ = efficacy; ?+ = probable efficacy; 0 = ineffective; - = worsen seizures; ? = unknown

The ultimate goal of epileptic pharmacotherapy is maintaining seizure-free status without unacceptable adverse events. However, less than half of patients do not achieve this goal. Monotherapy remains the treatment of choice for new-onset epilepsy. It reduces possible drug-drug interaction and adverse events (Leppik, 2000).

Antiepileptic drugs (AEDs) selection depends on epilepsy type. Broad spectrum AEDs such as sodium valproate, topiramate are effective for any types of seizure whereas, some drugs such as phenytoin, phenobarbital are effective only for some type of seizure furthermore, they can be deteriorate some type of seizure.

## PHARMACOLOGY OF PHENYTOIN

Phenytoin (PHT) or 5,5-diphenylhydantoin was synthesized by Biltz in 1908 and later on it has been found to elevate threshold to electrically induced seizure in cat by Putnam and Merritt in 1937. Furthermore in 1938, it was found to be effective against clonic seizure without sedation. Phenytoin is a white crystalline with a molecular weight of 252.3. A poorly water-soluble weak acid. Its $pK_a$ is 8.3. Its sodium salt has a weight of 274.3 (Kutt and Harden, 1999) (Fig. 1).

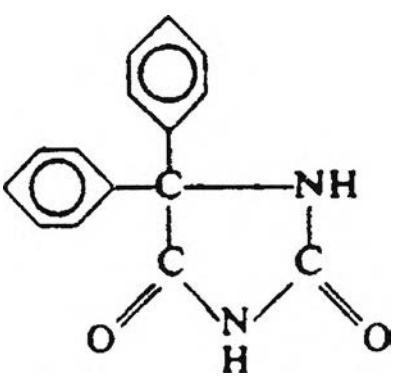


**Fig. 1** Chemical structure of phenytoin
(Browne and LeDuc, 2002)

**Dosage form of phenytoin**

Phenytoin was formulated into 3 dosage forms; tablet, capsule, and solution for injection. Phenytoin tablet presented as phenytoin base 50 mg per tablet (Dilanin Infatab®), capsule dosage form presented as phenytoin sodium 100 mg per capsule (Dilantin Kapseal® ), and parenteral dosage form presented as phenytoin sodium 50 mg per mL (Dilantin®) (Fun, 2005).

**Pharmacokinetics**

*Absorption*

The absorption rate of PHT varies somewhat with different formulations, peak plasma concentration usually appears within 4-8 hours from oral intake. In general, the bioavailability (F) of oral PHT is about 90 %.

*Distribution*

After intravenous (IV) administration, PHT is fairly rapid distributed to various tissue, maximum drug concentration in the brain is reached in 15 min. PHT passes the placenta, PHT concentration in the cerebrospinal fluid (CSF) usually equal the unbound concentration of the drug in plasma (10 % of the concentration in whole plasma), while those in saliva can be somewhat higher.

The apparent volume of distribution ranges from 0.5 to 0.8 L/kg in adults and from 0.8 to 1.2 L/kg in children. About 90 % of the phenytoin in plasma is protein bound. The percentage bound is lower in poor renal function, chronic liver diseases, pregnant women, and other diseases which cause hypoalbuminemia. Other drugs such as salicylates or valproate reduce phenytoin binding by competing for binding site.

The maximum plasma phenytoin level produced by doses of 300-400 mg/day is usually achieved in 5-14 days.

*Metabolism*

Various metabolic pathways of PHT were shown in Fig. 2. The metabolism of phenytoin involves extensive hydroxylation, mostly at one of its phenyl substitutes via an arene oxidation. There are evidence that the para-(4)-hydroxylation of the drug is mediated largely by cytochrome P 450 (CYP) C2 subfamily isozymes, CYP 2C9 and CYP 2C19 is the major and minor CYP for PHT metabolizing, respectively (Kutt and Harden, 1999).

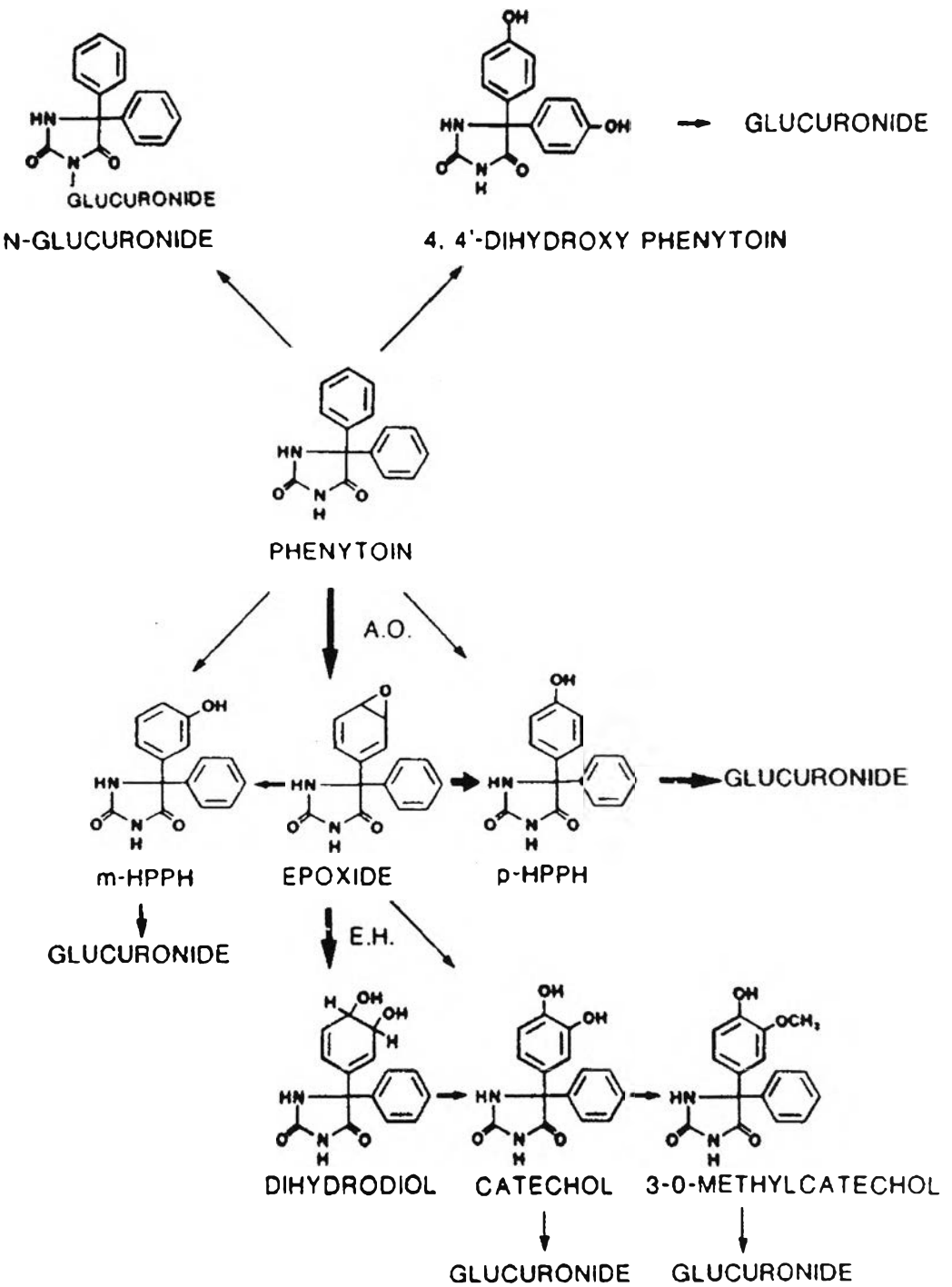


**Fig. 2** The metabolic pathways of phenytoin.

(Browne and LeDuc, 2002)

Phenytoin has unique pharmacokinetics. At therapeutic levels, phenytoin parahydroxylation exhibits first-order kinetics. In the upper therapeutic and toxic range, elimination changes from first-order to zero-order kinetics due to saturation of enzyme system. As a result, a small increase in dose results in toxic drug levels. Once phenytoin administration is stopped, toxic levels will decrease slowly as elimination follows zero-order kinetics. With continued excretion of phenytoin, elimination changes from zero-order to first-order kinetics and drug levels decrease more rapidly. (Chua, Venketasubramanian, Tjia et al., 2000) This becomes significant because clinically effective concentrations of phenytoin are often higher than its $K_m$ in the individual. Polymorphism of CYP 2C9 may account for alteration in metabolism. There are 2 major types of variations; slow (poor) metabolizers and fast (extensive) metabolizers. This variation may cause treatment failure or drug toxicity and thus requires close blood level monitoring.

There are many appropriate therapeutic ranges of phenytoin (Winter, 2001) according to its indications: for seizure control, therapeutic range is 10-20 mg/L. Approximately 50% of patients show decreased seizure frequency with phenytoin concentrations equal to or greater than 10 mg/L, and almost 90% respond with concentrations equal to or greater than 15 mg/L. For cardiac arrhythmias, the therapeutic range is 10-20 mg/L. Phenytoin is used infrequently to treat ventricular arrhythmias and most arrhythmias amenable to phenytoin therapy respond at concentration less than 20 mg/L.

*Elimination*

Clearance values for PHT show wide variations, ranging from 0.015 to 0.065 L/kg/h, the higher values being observed in children. The plasma half-life of PHT depends on its dose and preexisting plasma concentration. A 100 mg test-dose yielded half-life values of 8-15 hours and 250 mg dose values about 20 hours. The often quoted half-life value of 20 hours is usually found in adults receiving average dose of PHT.

**Clinical Pharmacokinetics: suggested sampling times**

As a general rule, intravenous loading doses are reasonably reliable in achieving the desired phenytoin concentrations, but oral loading and oral or intravenous maintenance regimens are less predictable. (Table 4)

**Table 4** Appropriate sampling time of phenytoin

(Winter, 2001)

| Administered dose | Suggested Sampling Time |
|---|---|
| Loading dose IV | > 2 hour after end of infusion |
| IV infusion | > 2 hour after end of infusion |
| IM (fosphenytoin) | > 4 hour after injection |
| Oral | About 24 hour after loading dose |
| IV (maintenance divided dose) | Trough |
| Oral divided dose (maintenance) | Timing not critical; trough suggested |
| Oral single daily dose | Trough recommended (morning sample probably acceptable with bedtime dosing if time after dose is consistent) |

**Pharmacodynamics**

PHT has been classified as a type I anticonvulsant which modified maximal electroshock seizures (MES), blocks sustained repetitive firing and prevents tonic-clonic and some partial seizures but is ineffective against pentylenetetrazole (PTZ)-induced convulsion and does not modified GABAergic synaptic transmission or the T-type calcium currents in the thalamic relay nuclei. (Kutt and Harden, 1999)

**Adverse Events**

Adverse events consisting of toxicity, idiosyncratic adverse events, teratogenicity, and chronic toxicity have been described. (Kutt and Harden, 1999)

Acute Toxicity

The acute toxicity of phenytoin is characterized by central nervous system (CNS) effects and resulted from a direct action of phenytoin at its site of action.

When plasma concentration of phenytoin approach 20 mg/L, side effects such as blurred vision and nystagmus could be observed. Disturbance of equilibrium and coordination could occur when plasma level approach 30 mg/L. At the plasma level of 40 mg/L, somnolence may occurs. Almost all patients have a normal clinical signs when plasma level of phenytoin is between 10-20 mg/L.

Phenytoin toxicity (as defined by clinical features) occurs in patients who have predisposing factors for toxicity such as hypoalbuminemia, chronic renal failure, hepatic dysfunction secondary to hepatitis or cirrhosis, genetic defects in phenytoin metabolism, and inhibition of phenytoin metabolism by other drugs.

Concentrations-related side effects may occur in many clinical symptoms. Nystagmus can be progressive from far lateral at phenytoin concentrations of 15 to over 20 mg/L or at concentrations greater than 50 mg/L. CNS depression, this can vary from mild sedation to an inability to concentrate and finally to confusion or coma. Most patients experience relatively mild effects at concentration of 5-15 mg/L; others tolerate phenytoin concentrations greater than 20 mg/L. Ataxia and impaired motor function are usually observed with phenytoin concentrations greater than 20 mg/L and become more frequent and obvious at concentration greater than 30 mg/L.

Idiosyncratic adverse events

Allergic skin rashes are the most frequent idiosyncratic effects of phenytoin, and occur in 5-10 % pf patients, but usually reversible.

Patients may also develop fever, mild lymphoadenopathy and hepatosplenomegaly, which might involve immunologic reaction (IgG – mediated).

Teratogenicity

The overall incidence of cleft lip and palate is 2% in the general population, 4% in the offspring of untreated epileptic women and 6% in the offspring of epileptic women treated with average dosages of anti-seizure medications. Polypharmacy increases the risk of theses major malformations to over 10% .

Roles of folate in phenytoin-mediated teratogenicity have been studied, phenytoin may alter serum folate possibly due to interference with folate absorption and biotransformation. Megaloblastic anemia may occurs. There are many evidences indicating that low levels of serum folate could underlie fetal abnormalities. In clinical evaluations, folate supplementation do not consistently prevent birth defects. However, folate supplementation helps to achieve an optimum outcome to pregnancy (Berg et al., 1995).

Chronic toxicity

There is negative cosmetic impact, gingival hyperplasia occurs in up to 40% of patients taking the drug and, if present, is evident in the first few months of therapy. It may be averted or improved by careful oral hygiene and may be related to a deficiency in salivary IgA.

Osteomalacia may occurs in patients taking phenytoin. Induction of vitamin D metabolism by phenytoin has been proposed to be and underlying cause. In addition, suboptimum exposure to sunlight may be predisposing factor as well (Kutt and Harden, 1999).

## PHARMACOLOGY OF VALPROIC ACID

Valproic acid is a member of conventional AEDs with broad spectrum activity that has been launched since 1978. It has a simple chemical structure. (Fig. 3)

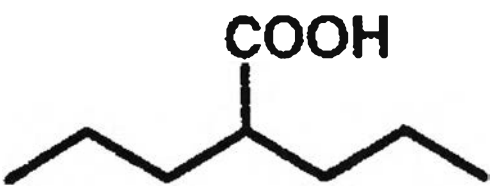


**Fig. 3** Chemical structure of valproic acid
(Levy et al., 2005)

### Dosage form of sodium valproate (SV)

Valproic acid was formulated into 3 dosage forms; tablet, oral solution, and sterile powder for injection, all of them are presented as sodium salt. Tablet dosage form can be divided into 2 types; immediate release tablet (Depakine®) is enteric coated tablet, consisting of sodium valproate 200 mg per tablet, extended release tablet (Depakine Chrono®) consisting of sodium valproate 333 mg, valproic acid 145 mg (equivalent to valproate 167 mg). Oral solution consisting of sodium valproate 200 mg per mL, and powder for injection consisting of sodium valproate 400 mg per vial (Fun, 2005).

### Pharmacokinetics

*Absorption*

No site specificity for absorption has been demonstrated and valproate is rapidly absorbed throughout the gastrointestinal tract Absorption from uncoated tablets or solutions is rapid and independent on gastric emptying rate. Peak plasma concentrations have been reported from a half an hour to 4 hours (fasting status). In contrast, absorption

from enteric coated is dependent on gastric emptying rate and there is thus a significant time-lag before absorption commences.

Food may delays rate of absorption but does not significantly affect total amount of drug absorbed as calculated from the AUC. In addition, drug administrations in patients and healthy volunteers have demonstrated bioavailability (F) close to 100 %.

*Distribution*

The volume of distribution ($V_d$) of valproate is largest in children and in patients on concurrent AEDs. It is usually around 8-10 liters. The drug is 90 % protein bound at therapeutic levels (mainly albumin), but this figure decreases at higher plasma levels and in the presence of high levels of circulating free fatty acids. The dose-blood level relationship is linear and therefore valproate may not require blood level monitoring.

Cerebrospinal fluid (CSF) levels of the drug are accurately reflected by free plasma valproate level. In brain tissue valproate levels fluctuate between 7 and 29% of plasma levels. However, valproate does not disperse equally to all brain but concentrate preferentially in brain area with high GABA transaminase (GABA-T) activity. Valproate freely crosses the placenta but secretion into breast milk, semen and saliva is low. When plasma valproate concentrations are between 40 and 100 mg/L (40-100 mcg/mL), the degree of protein binding is usually with the range 85-94 % (average 90%) in normal renal and hepatic function subjects (Product Information Depakine®: 20-21, 24).

*Metabolism*

Valproate is almost completely metabolized by the liver before elimination. In human, four main metabolic pathways have been reported: glucuronidation, β-oxidation, ω-oxidation, and $\omega_1$-oxidation (Davis, Peters, and McTavish, 1994; Product Information Depakine® : 28-30).

In case of very low dose, β-oxidation is the main metabolic pathway for valproate. However, with increasing dose (including therapeutically dose) glucuronidation is the major metabolic pathway. The ω-oxidation and $\omega_1$-oxidation appear to be of less importance than glucuronidation and β-oxidation (Figure 4-5).

All of metabolites were considered to show some antiepileptic activity in mice, but they are less potent than valproate itself on a molar basis.

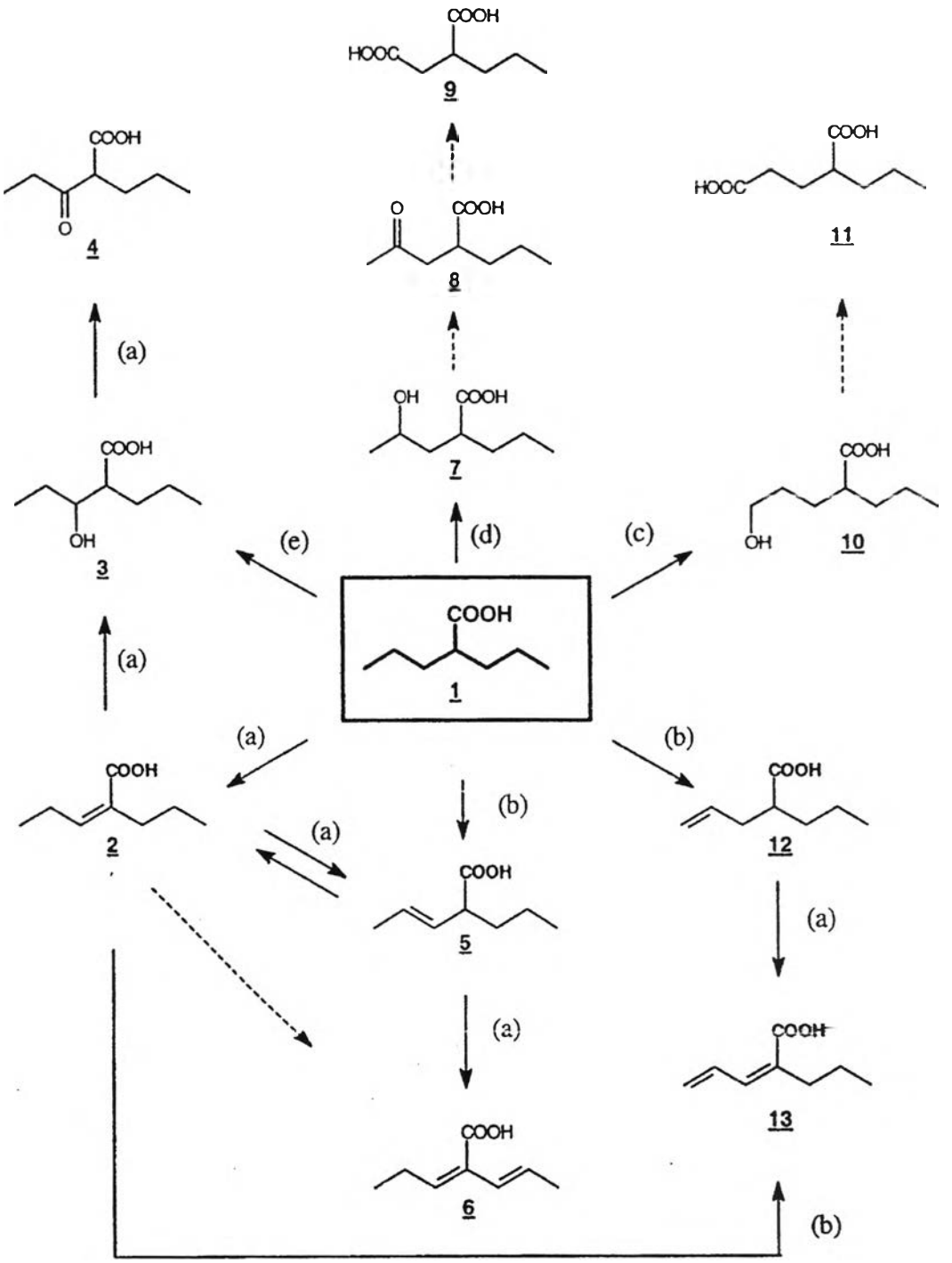


**Fig. 4** Phase I metabolic pathway of valproic acid

Valproic acid (1) and its metabolites involved in phase I metabolic pathways observed in humans: 2, 2-ene-VPA; 3, 3-OH-VPA; 4, 3-keto-VPA; 5, 3-ene-VPA; 6, 2,3'-diene-

VPA; 7, 4-OH-VPA; 8, 4-keto-VPA; 9, 2-PSA; 10, 5-OH-VPA; 11, 2-PGA; 12, 4-ene-VPA; 13, 2,4-diene-VPA. The putative characterized enzymatic pathways are as follows: (a) β-oxidation; (b) P450-dependent desaturation; (c) P450-dependent ω-hydroxylation; (d) P450-dependent (ω-1)-hydroxylation; (e) P450-dependent (ω-2)-hydroxylation. The *broken lines* indicates a metabolic route in which the details are not yet confirmed. (Levy et al., 2005)

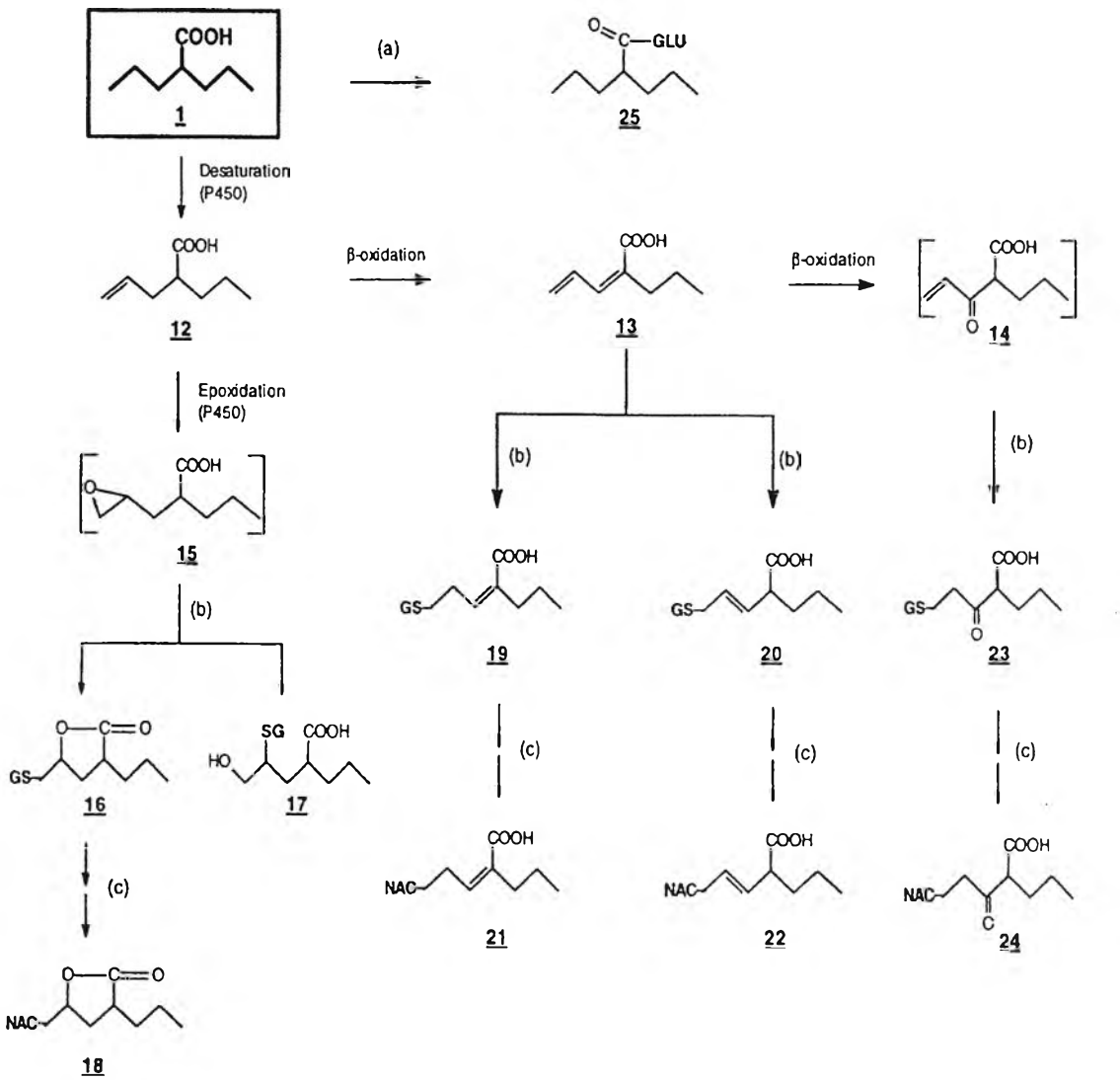


**Fig. 5** Phase I and Phase II metabolic pathway of valproic acid

Valproate (1) and phase I metabolites (12,13) involved in phase II metabolic pathways: 12, 4-ene-VPA; 13, 2,4-diene-VPA; 14, 3-keto-4-ene-VPA; 15, 4,5-epoxy-VPA; 16, 5-GS-4-OH-VPA-γ-lactone; 17, 4-GS-5-OH-VPA, 18, 5-NAC-4-OH-VPA-γ-lactone; 19, 5-GS-2-ene-VPA; 20, 5-GS-3-ene-VPA; 21, 5-NAC-2-ene-VPA; 22, 5-NAC-3-ene-VPA; 23, 5-GS-3-keto-VPA; 24, 5-NAC-3-keto-VPA; 25, VPA glucuronide. The putative enzymatic pathways are as follows: (a) glucuronidation; (b) glutathione

conjugation; (c) mercapturic acid pathway. Postulate intermediate compounds are shown in *square blankets.* (Levy et al., 2005)

*Elimination*

Plasma clearance is independent on the route of administration and is greater in children than adults. In healthy volunteers, clearance was within the range 7 to 11 mL/hr/kg. The elimination half life is variously quoted within the range 8 to 20 hours. Lower values may be found in children (Product Information Depakine®: 27 )

Half life is considerably reduced in patients on concurrent therapy with enzyme-inducing AEDs. However, longer half life may be seen in neonates, the elderly and in some pathological conditions.

Renal clearance is a minor route of elimination. 1-3 % of administered dose is excreted unchanged in the urine. In addition, there is wide interpatients variation in the urinary excretion pattern of valproate metabolites.

**Clinical Pharmacokinetics: suggested sampling times**

Due to rapid absorption, and the effects of circulating free fatty acids (FFAs) plasma valproate levels show considerable diurnal variation, making meaningful interpretation of single values from plasma monitoring difficult. Peak levels are often more than double trough levels. There is no general agreement on the most appropriate time of sampling (Product Information Depakine®: 22)

**Pharmacodynamics**

*Mechanism of action*

There are many hypothesizes explaining the mode of action of valproate. However, T-type calcium channels repetitive firing reduction and GABA neurotransmission enhancement are expected to be principle mode of actions of valproate.

*Toxicity*

Increased levels of GABA due to decreased or delayed metabolism may be responsible for the general CNS depression. The hyperammonemia results from valproate-induced increase in propionic acid that inhibit carbamyl phosphate synthetase I, the enzyme that catalyze the initial reaction in the urea cycle

Valproate toxicity may present as depression of central nervous system and respiratory tract. Reflexes decreased, coma, paradoxical seizures, nausea, vomiting, pancreatitis, hyperammonemia, elevation of transaminase enzymes (Davis, Peters, McTavish, 1994: Löscher, 2002).

## NEUROPSYCHOLOGY, COGNITION, AND THEIR ASSESSMENT

In the beginning of 20th century, attempt to measure expression of brain activity especially abstract thinking or subjective measurement still dominated the literature. The field of cognitive science encompasses all of the different approaches to study intelligent systems. Cognitive psychology and cognitive neuropsychology are two branches of cognitive science which study the same intelligence system. They differ in that cognitive psychology is the science of normal brain function whereas, cognitive neuropsychology is the science of brain dysfunction in individuals. Many psychological tests were developed and explained to measure activity of the brain (Ossetin, 1998; Getz and Lovell, 2004).

Cognitive function is higher-order behavior involving primarily the cortical structures of the brain to program adaptive behavior, to solve problems, memorize information and focus attention (Aldenkamp, De Krom, and Reijs, 2003). In neuropsychological theory, cognition or cognitive function is composed with *receptive functions* involving the abilities to select, acquire, classify, and integrate information; *memory and learning* refer to information storage and retrieval; *thinking* defined as any mental operation that relates two or more bits of information explicity or implicity. A host complex cognitive functions is subsumed under the rubric of thinking such as computation, reasoning and judgment, concept formation, abstracting and generalizing, ordering, organizing, planning, and problem solving; and *expressive functions* are the means through which information is communicated or acted upon such as, speaking, drawing or writing, manipulating, physical gestures, facial expressions, or movements, make up the sum of observable behavior. Mental activity is inferred from them. In addition, the higher cognitive functions of abstraction, reasoning, judgment, analysis, and synthesis tend to be relatively sensitive to diffuse brain injury, even when most specific receptive, expressive or memory functions remain essentially intact (Goodglass and Kaplan, 1983 cited in Lezak, 1999). Cognitive activity was originally attributed to a single function, intelligence. Early investigators treated the concept of intelligence as if it were a unitary variable which, like physical strength, increased at a regular rate in the course of normal childhood development (Binet and Simon, 1908; Terman, 1916 cited in Lezak 1995).

Attention is a part of cognitive functions study. A clear and universally accepted definition of attention has not yet appeared in the literature (Johnston and Dark, 1986 cited in Lezak, 1995). Rather, attention refers to several different capacities or processes that are related aspects of how the organism becomes receptive to stimuli and how it may begin processing incoming or attended-to excitation. Aspects of attention are more fragile and thus often of greater clinical concern. *Focused or selective attention* is probably the most studied aspect, and the one people usually have in mind when talking about attention. *Sustained attention or vigilance*, refer to the capacity to maintain an attentional activity over a period of time. *Divided attention* involves the ability to respond to more than one task at a time or to multiple elements or operations within a task, as in a complex mental task. It is thus very sensitive to any condition that reduces attentional capacity. *Alternating attention* allows for shift in focus and tasks.

Attention and concentration impairment are among the most common mental problems associated with brain damage. When impairment occurs, all the cognitive function may be intact and the person may even be capable of better than average performance, yet overall cognitive productivity suffers from inattentiveness, faulty concentration, and consequent fatigue.

The neuropsychological assessment plays a significant role in the diagnosis, prognosis, and treatment of neuropsychiatric disorders. A major goal of the neuropsychological assessment is to understand underlying cognitive processes through the quantification of behavior. This approach toward understanding brain behavior relationships has proved to be useful with a variety of patient populations, including those with dementia, traumatic brain injury, vascular dementia, epilepsy, and developmental disorders. The goals of neuropsychological examination are to determine an individual's cognitive and behavioral strengths and weaknesses, to interpret the finding from a diagnostic viewpoint, and to recommend viable treatment and rehabilitation resolution. The formal assessment portion of the neuropsychological evaluation usually involves the administration of a series, or batteries, of tests, selected to cover the range of behavior or area of cognitive functioning in question (Giordani, 1996). Importance of test selection depends on expected questions. Behavior cannot be considered in isolation, and skills are potentially affecting the ability. Clinical approaches toward the evaluation of cognitive

abilities vary among neuropsychologists, but all approaches constitute attempts to determine whether the patient demonstrates brain-based dysfunction. There are seven major cognitive domains will be examined; intelligence, attention, memory, executive functioning, language, motor functioning, and visuospatial and visuomotor. (Appendix A)

*Intellectual Processes.* General intellectual functioning has been defined in numerous ways, but it is broadly considered to be the capacity to learn from experience and to adapt to one's environment. For epilepsy, there is a wide range of abilities among epileptic patients, which extends between mental retardation and very superior level of functioning. Hence, attempts to answer a general question about intelligence level in epileptic populations are not well directed. Many studies indicated that, in general, no deterioration of intelligence occurs in a majority of epileptic patients except for certain groups. Assessment of intelligence has been beginning for many years, since the 1950's, the Wechsler scales, the WAIS and the WISC, have been the most commonly employed instrument for the assessment of intelligence in epileptic patients. The most commonly used set of tests that measures intelligence is the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III). This battery, which takes 90 – 120 minutes to administer, consists of several subtests examining a range of cognitive skills, including abstract solving ability, general fund of knowledge, vocabulary skills, and visuospatial organization. However, due to time constraints, limitation in patient's stamina, severity of cognitive impairment, or numerous other reasons, a shorter version of WAIS-III was developed. However, in practice, there are two major problems with assessing changes of intelligence over time. One is associated with the relative dependence of IQ scores on attained educational level. The other is practice effects of repeated IQ tests. Studies of recent outcome of the WAIS show a tendency for IQs to rise on the second testing, particularly for the Performance IQ (Matarazzo and Herman, 1984 cited in Ossetin, 1998).

*Attention.* From neuropsychological perspective, attention is a complex cognitive activity that makes it possible to process meaningful stimuli. Attention is an important cognitive skill because it is a prerequisite for successful performance in other cognitive domains (Getz and Lovell, 2004).

*Executive function.* It is a multi-faceted construct that has been conceptualized from a variety of contexts. Executive functions include the ability for planning, directing

and maintaining attention, organization, abstract reasoning and problem-solving, self-regulation, and motor control.

Both attention and executive function can be measured by the same test, Stroop Interference test or Stroop Color Word Test. Stroop can measure selective attention, cognitive flexibility, and ability to inhibit a dominant response. The Stroop is a quick measure that is used frequently in screening for brain damage.

*NEUROPSYCHOLOGICAL ASSESSMENT EQUIPMENTS*

**Wechsler Abbreviated Scale of Intelligence (WASI®).** It was developed to meet the demands of a quickly and accurately measure of individual's intellectual functioning and for screening purposes in clinical, psychoeducational, and research settings. The WASI® is designed for aged from 6 to 89 years. The WASI® is nationally standardized and yields the three traditional Verbal, Performance, and Full Scale IQ scores. The scale is also linked to the *Wechsler Intelligence Scale for Children-Third Edition* (WISC-III®) and the *Wechsler Adult Intelligence Scale-Third Edition* (WAIS®). (Appendix B)

The WASI® consists of four subsets; Vocabulary (V), Block Design (BD), Similarities (S), and Matrix Reasoning (MR). These subsets are similar in format to their WISC-III and WAIS-III. The four subsets of the WASI® tap various facets of intelligence, such as verbal knowledge, visual information processing, spatial and nonverbal reasoning, and crystallized and fluid intelligence.

Vocabulary- The WASI® vocabulary is a measure of the individual's expressive vocabulary, verbal knowledge, and fund of information. In addition, it is a good measure of crystallized intelligence and general intelligence or g. It also taps other cognitive abilities, such as memory, learning ability, and concept and language development. In practice, the examinee must define several assigned words.

Block Design- The WASI® block design taps the abilities related to spatial visualization, visual-motor coordination, and abstract conceptualization. It is a measure of perceptual organization and general intelligence. The score of test reflects the individual's ability to visually perceive and analyze abstract figures and to construct the whole from the component parts. In practice, the examinee is presented with a picture of a geometric design and must reproduce the design by using colored blocks in a restricted time.

Similarities- The WASI® similarities is a measure of verbal concept formation, abstract verbal reasoning ability, and general intellectual ability. The similarities score is a measure of the individual's ability to see relationships between objects or concepts and to generalize the relationships into a single concept. In practice, the examinee is presented with two items and is asked how they are alike.

Matrix Reasoning- The WASI® matrix reasoning is a measure of nonverbal fluid reasoning and general intellectual ability. Matrix reasoning performance reflects the individual's ability to mentally manipulate abstract symbols and to perceive the relationship among them. In practice, the examinee is presented with several pictures that are missing a part and is asked to select the correct part from among several choices.

WASI® can be used to estimate IQ scores rapidly and efficiently when administration of a full battery is neither feasible nor necessary or as a screening to determine if an in-depth evaluation is necessary or retesting individuals who received a comprehensive evaluation at an earlier time when time is limited. Obtaining estimates of current cognitive functioning for individuals referred to psychiatric, psychological, or psychoeducational evaluations, obtaining estimates of IQ scores for vocational and rehabilitation purposes, and obtaining estimates of IQ scores for research purposes, such as preexperimental matching of cognitive ability.

All Wechsler scales are designed to measure general intellectual ability and its sub domains. In practice, clinicians are often required to describe the strengths and weaknesses in cognitive functioning exhibited by the individual. Here, the WASI IQ scales and subtests are described in terms of the cognitive function tapped by each. The FSIQ is the overall estimate of an individual's general level of intellectual functioning. The VIQ of the WASI® is a measure of acquired knowledge, verbal reasoning, and attention to verbal information. The PIQ is a measure of fluid reasoning, spatial processing, attentiveness to detail, and visual-motor integration (Psychological Corporation, 1999).

**Stroop Color Word test (SCWT)**

Since being introduced to American psychology, the Stroop Color-Word Test has been used extensively in studies of perception, cognition, and response inhibition. The Stroop procedure has been called "the gold standard of research in attention" (Block, 2005). Stroop test is the test for divided attention, ability to ignore extraneous information while focusing on specific stimuli. This task measures both executive functioning and divided attention. It has been strongly suggested that one important function of frontal lobes is inhibition, the Stroop test may suggests about normality of frontal lobes (Andres and Van Der Linden, 2004). Moreover, slowed performance on the interference subtest has thus far been interpreted to be reflective of difficulty with the ability to resist interference, a cognitive function associated with frontal cortical integrity (Gruber et al., 2002). Generally, the Stroop task consists of two conditions. – one that the task demands should define the response tendency that must be suppressed. In a second neutral condition the irrelevant piece of information does not, or to a lesser extent, evokes the conflicting response tendency. This test involves three parts. In the first part, the examinee is presented with a list of name of colors, which they must read aloud. During the second part, the examinee is required to name the color of a series of X's. In the third part, the examinee is presented with a list of names of colors that are printed in different-colored ink and is asked to name the color of the ink, ignoring the word. The difference in performance between the two conditions, or the "Stroop interference" score, can be used as a measure of selectivity. Patterns of interference are determined by the relative strengths of the functional connection between input and output representations. For example, normally the connection between a color-word stimulus input and the tendency to read the word is stronger than the connection between that same input and the tendency to name the color the word has been written in (Kenemans, Wieleman, Zeegers, and Verbaten, 1999).

**Profiles of Mood States (POMS)**

The POMS is a self-administered 65-items adjective checklist that measures mood disturbance across six dimensions: depression/dejection, tension/anxiety, fatigue/inertia, confusion/bewilderment, anger/hostility, and vigor/activity. It has strong evidence of reliability and validity, has been used in several studies of epileptic patients, and has been found to have moderate to strong correlation with Health Related Quality of Life (HRQL) among epileptic patients (McNair et al, 1992; Vicky et al., 1992; Baker et al., 1993; Dodrill et al., 1993; Devinsky et al., 1995 cited in Elixhauser, 1999). Internal consistency reliability for the POMS in the study of McNair (1992) (Elixhauser, 1999: 16) ranged from 0.77 to 0.94 (0.95 for the entire scale).

## EPILEPSY AND NEUROPSYCHOLOGICAL EFFECTS

Problems with cognition are common in epileptic patients. The results from the study of 'Cognitive Function Survey' revealed that 44% of epileptic patients complained of difficulty learning, 45% felt that they were slow thinkers, 59% felt sleepy or tired, and 63% felt AEDs effects prevented them from achieving activity or goals (Meador, 2006).

Although individual epileptic patients are often found to have normal or superior intellectual capabilities, populations with epilepsy tend to have a lower level of intellectual performance (Vining, 1987). Most of epileptic patients lead normal lives with few or no cognitive or psychiatric disturbances. However, some patients develop significant cognitive deficits, especially in the domain of attention, memory, and motor speed. Behavioral problems in epileptic patients may involve anxiety, depression or even psychoses. Epileptic patients whose seizures are well controlled by monotherapy usually have no dramatic problems with cognitive function. Cognitive function is a complex interaction of motivational, intellectual, and discrete mental ability.

*Intelligence.* Patients with well-controlled epilepsy rarely suffer a significant impairment in global intellectual functioning as assessed by IQ tests. There are several factors associated with lower IQ, including an identifiable neurologic etiology of the seizures, such as structural lesions. Moreover, lower IQ scores are involved with generalized tonic-clonic seizures (GTCS), episodes of status epilepticus, a very high number of GTCS, earlier age of chronic seizures onset and frequent subclinical epileptiform discharge, especially for generalized discharges.

*Attention and memory.* Epileptic patients show impaired sustained attention on vigilance tasks. Disruption in attention or reaction time can occur in relation to concomitant EEG discharges. Risk factors for memory impairment include temporal lobe focus, frequent generalized seizures, earlier age of onset, longer duration of seizure, a concomitant structural lesion, and episodes of status. This deficit affects to every day life of patients, a study of Thompson and Corcoran (1992) revealed different of 'Top five' memory problems between epileptic patients and non epileptic patients. (Table 5)

**Table 5** The top five memory problems of epileptic and non-epileptic patients (Thompson and Corcoran, 1992)

| Epileptic patients | Non-epileptic patients |
|---|---|
| 1. Tip-of-the-tongue (43%) | Going back to check (20.5%) |
| 2. Going back to check (39%) | Forgetting where you have put things (18.5%) |
| 3. Forgetting where you have put things (33%) | Forgetting name (14%) |
| 4. Forgetting name (31%) | Tip-of-the-tongue (14%) |
| 5. Forgetting you were told something (30%) | Rambling on to speak about unimportant things (11%) |

From a recent study in temporal lobe epileptic patients of Mameniskiene and colleague (2006), uncontrolled seizures, especially with ictal impairment of consciousness, can be a significant factor in accelerated decay of memory, although subclinical interictal epileptiform EEG activity may also be relevant.

*Language*. Word finding difficulty or even clinical anomia can occur in patients with left temporal lobe seizures.

*Executive functions*. Executive functions include complex problem solving, set shifting, inhibition, sequencing, and cognitive speed. Complex problem solving and cognitive flexibility are often impaired in epilepsy.

*Sensorimotor and perceptual areas*. Epileptic patients may have lengthened reaction time as well as slowing of pure motor speed. Impaired of motor speed and coordination are common in epilepsy, especially in GTCS patients.

*Visuospatial ability*. Impaired spatial analysis and constructional ability may occur in epileptic patients. Tachistoscopic presentation may be more sensitive and may differentiate left from right temporal lobe patients more reliable than traditional constructional tests. (Table 6)

**Table 6** Domains of cognitive functioning affected by epilepsy

(Perrine and Kiolbasa, 1999)

| Domain | Affected functions | Functions not affects |
|---|---|---|
| **Language** | Anomia<br>Fluency/word generation<br>Oral reading | Comprehension<br>Repetition<br>Writing |
| **Attention** | Simple attention<br>(digit span)<br>Simple reaction time<br>Sustained concentration<br>Vigilance | Complex attention<br>Divided/choice reaction<br>time |

(continued...)

**Table 6** Domains of cognitive functioning affected by epilepsy (continued)

| Domain | Affected functions | Functions not affects |
|---|---|---|
| **Memory** | Consolidation and delayed recall<br>Verbal memory (e.g. paragraphs)<br>Verbal learning (e.g. word lists/pairs)<br>Nonverbal memory (e.g. designs, faces) | Remote memory<br>Factual information |
| **Executive systems** | Concept formation<br>Preservation<br>Cognitive flexibility<br>Alternation of cognitive set | Impulse control<br>Self-monitoring |
| **Visuospatial** | Most areas not affected | Constructional ability<br>Perception and integration<br>Neglect, hemi-inattention |
| **Sensory/integrative** | Most areas not affected | Tactile perception<br>Praxis<br>Cross-modal integration |
| **Motor** | Fine motor dexterity<br>Motor sequencing<br>Psychomotor speed | Gross motor strength<br>Tone, reflexes, coordination |
| **Intelligence** | Varies | Varies |

In the molecular level, Jokeit and Ebner (2002) found the relationship between effects of chronic epilepsy on intellectual functions. This finding indicates an intractable and prolong epilepsy may cause disturbance of brain electric and neurochemistry via induction of neuronal loss and metabolic dysfunctions.

Clinical practice, refractory temporal lobe epileptic patients (TLE) are the high risk group for mental and cognitive impairment. The right-sided temporal lobe epilepsy are frequently impaired in visuo-spatial retention tasks; patients with left-sided temporal lobe epilepsy may exhibit deficits of verbal memory (Ivnik et al., 1998 cited in Jokeit and Ebner, 2002)

Elger and others (2004) reported that cognitive profiles in epilepsy were as heterogeneous as epileptic syndromes. Causes, topography of epileptogenic areas, pathogenetic mechanisms, and the diverse features characterizing the clinical course all contribute to the effect on cognition. (Table 7), (Table A1 in appendix) In general, chronic epilepsy impairs cognition, but it also induces processes of compensation such as functional reorganization, behavioral compensation. There are three major factors which influence cognition in chronic epilepsy syndromes.

*Morphological factors* consisting of potentially progressive lesions e.g. tumor, encephalitis, paraneoplastic lesions; broadly stationary lesions e.g. hippocampal sclerosis, focal cortical dysplasia, post-traumatic lesions; and epilepsy surgery which largely irreversible. Different pathologies underlying the epileptic focus, even at the same anatomical site, can have different cognitive consequences. In surgical, hippocampal sclerosis was associated with greater impairment in intelligence, academic achievement, language and visuospatial functions and memory than others. Severity of cognition deficit can be related to the extent of the lesion. For instance, in a study of children and adolescent with refractory partial seizures caused by malformations of cortical development, diffuse cortical dysplasia was associated with a more severe deleterious effect on intellectual functioning than circumscribed lesions.

*Clinical and demographic factors* consisting of age of onset, sex, duration of epilepsy, lateralization or topography of epileptogenic area. Ictal cognitive and behavioral features are well recognized. The biggest impact of seizures on cognition, is through postictal effects, possibly via the disruptive influence of neuronal discharge on long-term potentiation involved in learning. Studies show that seizure type has a determining effect on the patient's cognitive profile, but the findings are inconsistent.

*Functional factors* consisting of antiepileptic drugs, psychiatric comorbidity, seiures, interictal epileptic discharges which largely reversible. There was a first report described the cognitive and behavioral side effect of bromide in 1850. More recent studies have shown consistently that antiepileptic treatment can have adverse cognitive consequences, although the effect can be subtle.

Adverse events were especially prominent in patients receiving polytherapy. For instance, one study found carbamazepine monotherapy to have little effect on cognition and psychomotor function, but significant impairment when it was added to an existing monotherapy regimen (Gillham, Williams, Wiedmann, Butler, Larkin, and Brodie, 1998 cited in Kwan and Brodie, 2001). High circulating antiepileptic drugs concentration is another potentiating factor. Most studies have shown that cognitive functioning is best when drug concentrations are within standard target ranges, and that high drug dosages and concentrations are associated with impaired intellectual functioning. Among the established AEDs, phenobarbital seems to have the greatest potential for cognitive and behavioral toxicity. Dose-related impairment occurs in attention and vigilance, reaction time, short-term memory, performance IQ. Phenytoin can cause decline in concentration, memory, mental speed, visuomotor functions, and intelligence. Although deficits seem to be dose related, they were seen even at drug concentration within the target range. Suggested behavioral dysfunction with phenytoin included decreased motor speed, anxiety, aggression, depression, and fatigue. Furthermore, Brodie and Kwan (2001) explained additional factors contributing to cognitive and behavioral impairment in epilepsy.

*Psychosocial factors.* Epilepsy has long been a misunderstood and stigmatizing disorder. In a survey carried out in USA in 1979, 92% of those interviewed thought that epilepsy was not a form of insanity, but only 79% believed that epileptic patients should be employed, and 89% would not object to their children playing with others who had epilepsy (Caveness and Gallup, 1980 cited in Kwan and Brodie, 2001). For quality of life aspect of epileptic patients, Baker and colleagues (2000) surveyed more than 5000 patients living in 15 European countries and found that 51% felt stigmatized. Such undoubtedly affect personal development, including self-esteem, mood, behavior, and cognitive abilities.

**Table 7** Type of epilepsies, their cognitive impairment pattern, and long-term cognitive outcome.
(Elger, Helmstaedter, and Kurthen, 2004)

| **Type of epilepsy** | **Characteristic deficit** | **Long-term cognitive development** |
|---|---|---|
| *Idiopathic epilepsies:* Juvenile myoclonic epilepsy | Frontal lobe deficit (mild) | Largely unknown (presumably favourable) |
| Idiopathic generalized epilepsy with absence seizure or GTCS | Attentional problems (mild) | Largely unknown |
| Benign epilepsy with centrotemporal spikes | Heterogeneous (mild) | Mostly favorable (dependent on persistence of interictal eileptiform discharge?) |
| Idiopathic occipital-lobe epilepsy | Heterogenous (mild) | Unknown |
| *Symptomatic or cryptogenic epilepsies:* Continuous spike-waves during sleep | Variable (diffuse or frontal deficits) | Variable (worse with long duration) |
| Landau Kleffner syndrome | Auditory agnosia, subsequence loss of expressive language functions | Variable (worse with earlier onset); language recovery possible |
| West syndrome | Retardation, regression (autism) | Unfavourable, retardation, reduced intelligence |
| Lennox-Gastaut yndrome | Retardation, Intellectual deterioration | Unfavourable, retardation (worse with earlier onset) |
| Frontal-lobe epilepsy | Impaired executive functions, attention deficits | Largely unknown |

**Table 7** Type of epilepsies, their cognitive impairment pattern, and long-term cognitive outcome.

(Elger, Helmstaedter, and Kurthen, 2004) (continued)

| **Type of epilepsy** | **Characteristic deficit** | **Long-term cognitive development** |
|---|---|---|
| Temporal lobe epilepsy | Material-specific episodic memory impairment | Very slow deterioration (dominant-side ALT: acceleration of deterioration) |
| Parieto-occipital epilepsy | Largely unknown (variable) | Largely unknown (heterogenous) |

GTCS = Generalized tonic clonic seizures; ATL = Anterior temporal lobectomy

## ANTIEPILEPTIC DRUGS AND NEUROPSYCHOLOGICAL EFFECTS

In human, a major factor complicating the testing of cognitive function is concomitant treatment with AEDs. Only a few studies have examined the performance of spontaneous seizing animals exposed to AEDs. There are two possible explanations; seizure-induced progressive network organization should be slowed or stopped and suppression of clinical and subclinical seizures should eliminate their direct effect on cognitive processing (Majak and Pitkänen, 2004). The study of AEs of AEDs on cognition in epileptic patients is a complex issue because AEs and benefits may compensate each other. For instance, AEDs may well impair memory, but they also bring about benefits to memory through their seizure suppression. Hence, should be taken into consideration of risk to benefit ratio.

AEDs exert their anticonvulsant effects by interfering with brain processes that involve structures that are also involved in learning, memory, and emotional behavior (Sankar and Holmes, 2004). Though there are many studies demonstrating behavioral effects of AEDs in healthy population or epileptic patients, the exact mechanisms of AEDs-induced cognitive and behavioral dysfunction remain to be investigated (Meador et al., 1990; Meador, 1991; Aldenkamp et al., 1994; Meador et al., 1995).

*Conventional AEDs*

Slowing of mental or motor speed and attentional deficits are well known adverse effects of the frequently used AEDs; CBZ, PB, and PHT. It is generally assumed that these AEDs do not specifically impair memory and that patients' memory complaint are secondary to the changes in their attentional level or mental processing speed induced by AEDs (Jokeit, Krämer, and Ebner, 2005).

In animal models, administration of GABA-related drugs; PB, triazolam, and chlordiazepoxide significantly disrupted performance by increasing error of omission, whereas TGB, VPA, and GBP did not. The sodium channel blocking drugs CBZ increased errors of omission at relatively high dose, whereas the sodium channel blocking agents; PHT, TPM, and LTG were without significant effect (Shannon and Love, 2005).

**Benzodiazepines:** the data from benzodiazepine antagonist, flumazenil has been shown to improve cognitive performance in hepatic encephalopathy in humans. Holley and others suggests that effects of benzodiazepines on memory and learning could be related to an effect on attention. (Holley et al, 1995 cited in Sankar and Holmes, 2004)

A 2-weeks double-blind crossover studies in volunteers reveals effects of clobazam on concentration and mental speed especially decision making (Trimble, 1987).

**Carbamazepine:** may have some adverse effects on task performance, although the impairment is less with carbamazepine than with phenytoin or phenobarbital. Data from animal study demonstrates that carbamazepine had no effects on learned taste aversion (Smith, 1983 cited in Sankar and Holmes, 2004). Zaccara and colleagues (2004) explained CBZ toxicity on vestibulocerebellar and brain stem dysfunction (i.e. ataxia, nystagmus, mental status changes). Phenytoin also has this toxicity too. A 2-weeks double-blind crossover studies in volunteers reveals effects of CBZ on concentration especially increased error in Stroop task and visuomotor speed (Trimble, 1987).

**Phenobarbital**: since phenobarbital is the oldest synthetic AEDs, it has been one of the most extensively studied. There are many studies in animal model which focused on effects of drug exposure on brain growth and behavior. Researchers have found that administration of phenobarbital to rat pups results in significant decreases in brain weight and DNA, RNA, protein, and cholesterol concentrations. In addition, it has been found to selectively impair short-term memory; higher concentrations appear to be more detrimental to test performance. Memory concentration and symbol manipulation also are affected, even when blood levels of the drugs are within the therapeutic range. Chronic exposure of phenobarbital leads to reduced cell survival and decreases in number and length of dendritic branch of cultured mouse spinal cord neurons. The study of Mikati and others confirm that animals receiving phenobarbital performed water maze significantly worse than saline treated group. Furthermore, phenobarbital has deleterious effects on cognition when being administered following an acute insult, such as status epilepticus. (Mikati et al., 1994 cited in Sankar and Holmes, 2004). Furthermore, human data revealed that PB can affect psychomotor speed, vigilance, cognitive speed, memory, concentration, and IQ. There is strongly evidence about PB-induced hyperactivity and irritability in children (Perrine and Kiolbasa, 1999).

**Phenytoin**: although there is a long-standing use of phenytoin, little is known about the effects of phenytoin on cognitive function in animals. In high dose, it impairs the ability of rat to push lever at scheduled interval, affected performance on neuropsychological test of problem solving and visuomotor tasks. Ability to pay attention also impaired. Impairment, especially in motor or timed activities, is greater when blood levels are in the upper reaches of the therapeutic range. Sudha et al. (1995) studied chronic effects of phenytoin on learning and memory impairment. Although it was conducted in animals, the probable mechanisms shown could be extrapolated to human. The results indicated that, chronic administration of phenytoin leads to a reduction of acetylcholinesterase (AchE) but, an increase in serotonin (5-HT), key neurotransmitter in memory role, in the hippocampus and striatum region of Wistar rat brain. Hence, impairment of learning and memory processes could subsequently occur. However, chronic administration of phenytoin to rats during first month of life had no unfavorable effect on water maze performance when the animals were tested as adults.

In a double-blind, randomized crossover, monotherapy study in healthy volunteers, CBZ and PHT were examined for cognitive decline effects. The results revealed no overall differences between the two drugs. However, 52% of the variables were statistically significantly worse on AEDs compared with nondrug condition (Meador, Loring, Allen et al., 1991; Meador, Loring, Abney et al., 1993 cited in Motamedi and Meador, 2003). In other studies, a 2-weeks double-blind crossover studies in volunteers reveals effects of PHT on many cognitive performance test e.g. memory, concentration motor speed and mental speed. In addition, a high plasma levels of PHT has a correlation with impairment of memory, a picture recall task (Trimble, 1987).

**Valproate**: has shown no effect on learning tasks when added to preexisting therapy, and produced minimal adverse effects on psychological tests. However, tremor is a common AEs in VPA-receiving patients. VPA-induced tremor may presented as an involuntary, rhythmic, oscillatory movement of a body part. These AEs do not correlate with plasma levels although tremor is usually observed at dosage greater than 750 mg/day (Zaccara et al., 2004). In direct comparisons with phenobarbital, valproate exhibits favorable cognitive profiles in children. Study comparing between phenobarbital and valproate on cognition in rats showed deleterious effects in phenobarbital-treated group.

In a study of active avoidance, valproate calcium (in the dose without anticonvulsant activity) had minimal effects on learning impairment induced by electroconvulsive shock.

*New generation of AEDs*

After breakthrough of new generation AEDs, felbamate, in 1993. There are many new AEDs with improved profiles of pharmacokinetics and pharmacodynamics than those of conventional AEDs launched in the market. However, in long-term study, some defects of these new generation AEDs could probable be discovered.

**Felbamate**: poses a problem for long-term investigation of its cognitive side effects because of the association with increase risk of severe hepatotoxicity. Common side effects of felbamate are somnolence, fatigue, dizziness.

**Gabapentin**: has been shown to have beneficial on mood as add-on therapy. In one double-blind study in healthy volunteers, the effects of gabapentin were compared with carbamazepine. Eight of the 31 neuropsychological testing parameters were significantly better than those of carbamazepine. The mechanisms of action of gabapentin do not fit with the model of classical AEDs. From several animal studies, gabapentin shows beneficial effects in status epilepticus and does not contribute to impairment or enhancement in learning in animals. (Sankar and Holmes, 2004)

**Lamotrigine**: was not associated with any adverse cognitive effects in a double-blind, placebo-controlled crossover study. Lamotrigine-treated patients demonstrated better performance in attention, memory, affective symptoms.

**Levetiracetam**: few formal data exist on incidence of cognitive side effects of levetiracetam. Levetiracetam does not exert its anticonvulsant effects by conventionally understood impact on neuronal excitability. This compound has similar structure to nootropic agents, which have produced cognitive enhancement in certain models of learning and memory. The structure analogs piracetam and etiracetam were shown to have a positive effects on learning and memory more than two decades ago (Bryant, Petty and Byrne, 1973: Wolthuis, 1981 cited in Sankar and Holmes, 2004). A 12- to 16- week levetiracetam treatment was noted to lead to greater than 1.5% incidence of anxiety, depression, emotional lability, and nervousness.

**Oxcarbazepine**: effects on cognitive function are not clear due to the lack of published data. Oxcarbazepine did not differ from phenytoin on tests of memory, attention, and psychomotor speed in a randomized, double-blind study.

**Tiagabine**: the overall effects of tiagabine is GABAergic neurotransmission enhacement. Treatment with tiagabine has resulted in impairment of Morris water maze performance test. (Schmitt and Hiemke, 2002 cited in Sankar and Holmes, 2004)

**Topiramate**: its mechanism involved AMPA and kainate subtypes of glutamate, an excitatory neurotransmitter, receptors. Clinical studies have demonstrated the negative effects of topiramate on cognitive function, including impaired concentration and memory, slowed thinking, word finding difficulties (Mula et al., 2003).

**Zonisamide**: in limited studies, zonisamide at 50 mg/kg did not affect spontaneous alternation behavior and active avoidance performance in mice. However, zonisamide impaired the acquisition of step-down passive avoidance behavior in mice.

Recently, with an advance neuropsychological testing methods, a relative cognitive effect of AEDs and effects of AEDs on cognition were clarified by head-to-head comparisons; CBZ is similar to PHT (Meador et al., 1991) and VPA (Coenen et al., 1995). PHT has a worse motor speed performance than CBZ (Aldenkamp et al., 1994) but, similar to VPA (Meador et al., 1995). PB has a worse AEs profile than CBZ, PHT, and VPA (Meador et al., 1995). LTG has better AEs profile than CBZ (Meador et al., 2001). TPM (correctly anticonvulsant dose) is slightly worse than VPA (Meador et al., 2003) and has a worse AEs profile than GBP and LTG (Martin et al., 1999).

In 2002, Meador had conclusively suggested numerous measures to reduce AEDs-induced cognitive adverse events, they are; treatment of underlying diseases, slow initial AED titration, use lowest AED dose possible, start with monotherapy of AED if possible, avoid known adverse events AEDs (e.g., PB), avoid pharmacokinetics interactions, balance all factors with best seizure control, confirm seizure diagnosis if patient is refractory to AEDs and consider epilepsy surgery early in refractory patients (Meador, 2002).