CHAPTER II
REVIEW OF LITERATURE

Epilepsy

Definition

Epilepsy may be diagnosed after a child has two or more unprovoked seizures. The definition of unprovoked is complex. Unprovoked implies that there has been no concurrent illness or acute brain injury closely associated with the seizures. Thus recurrent seizures immediately after a head injury or associated with drug intoxication or with fever do not qualify for the diagnosis of epilepsy. Some specific provoking factors leading to reflex seizures are permitted- for example, seizures provoked by patterns and flashes from video terminals for children with photosensitive epilepsy or seizures provoked by reading complex texts for those with primary reading epilepsy. Provoking factors related to personal activity, such as sleep deprivation or severe emotional stress, are generally not viewed as significant in the diagnosis of epilepsy unless they are extreme.(12)

Seizure Type and Epilepsy Type

The definition of epilepsy allows for a tremendous variety of disorders. The age of onset, etiology, severity, comorbid conditions, response to medication, and clinical course vary widely. There are two main ways of grouping patients to bring and ordered approach to classification, treatment, and prognosis—seizures type and epilepsy type. All children with epilepsy have seizures, and there are a variety of seizure types. The International League Against Epilepsy has defined the seizure types listed in Table I [Commision on classification and Terminology of the International League Against Epilepsy, 1981]. (6,12)

Table I   International Classification of Epileptic Seizures

   I. Partial seizures (seizures begin locally)

      A. Simple (without impairment of conciousness)

         1. with motor symptoms

         2. with special sensory or somatosensory symptoms

         3. with psychic symptoms

      B. Complex (with impairment of consciousness)

         1. simple partial onset followed by impairment of consciousness – with or without automatisms

         2. Impaired consciousness at onset- with or without automatisms

      C. Secondarily generalized (partial onset evolving to generalized tonic-clonic seizures)

  II. Generalized seizures (bilaterally symmetrical and without local onset)

      A. Absence

      B. Myoclonic

      C. Clonic

      D. Tonic

      E. Tonic-clonic

      F. Atonic

      G. Infantile spasm

 III. Unclassified seizures

 IV. Status epilepticus

Complied from the Commission on Classification and Terminology of the International League Against Epilepsy, 1981

A given seizure type may occur with many different associations. For example, a 2-year-old child with severe mental handicap may have generalized tonic-clonic seizures that are completely resistant to medication, or normal teenager may have the same seizure type that is completely suppressed by medication. Therefore factors beyond seizure type allow a more meaningful diagnosis. A growing number of epileptic syndrome have one or more seizure types, often with a characteristic interictal EEG. Each syndrome has a defined group of etiologies, sometimes a clear response to specific treatments and

sometimes a defined clinical course and prognosis. A list of current syndromes recognized by the International League Against Epilepsy is presented in Table II [Commission on Classification and Terminology of the International League Against Epilepsy, 1989]. In adult-onset epilepsy, localization-related syndromes are most common and are usually symptomatic of an underlying, localized, structural abnormality. Although children have similar disorders, there are many other important syndromes. The idiopathic partial and generalized syndromes all have their onset in childhood and genetic influences are significant. In idiopathic epilepsies there is assumed not to be a major structural cause a polygenic trait is considered important. Idiopathic epilepsies tend to have onset in childhood or adolescence and have characteristic electroclinical features as seen in Table III The generalized symptomatic syndromes of childhood account for the majority of intractable epilepsy in children. (12,13)

The International League Against Epilepsy chose to classify febrile convulsions as a special syndrome. Febrile seizures are the most common convulsion event in the human species. Since seizures in this disorder are provoked by fever, the disorder does not fit well with the usual definition of epilepsy, and few of these children later develop unprovoked seizures.

Table II International Classification of Epilepsies and Epileptic Syndrome and Related Seizure Disorders

Localization –related (local, focal, partial) epilepsies and syndromes

Idiopathic (with age-related onset)

Benign childhood epilepsy with centrotemporal spikes

Childhood epilepsy with occipital paroxysms

Primary reading epilepsy

Symptomatic

Chronic-progressive epilepsia patialis comtinua

Syndromes characterized by seizures with specific modes of precipetation

Temporal lobe epilepsies

Frontal lobe epilepsies

Parietal lobe epilepsies

Occipital lobe epilepsies

Cryptogenic

Generalized epilepsies and syndromes

Idiopathic (with age-related onset)

Benign neonatal familial convulsions

Benign neonatal convulsions

Benign myoclonic epilepsy in infancy

Childhood absence epilepsy

Juvenile myoclonic epilepsy

Epilepsy with grand mal seizures on awakening

Other generalized idiopathic epilepsies

Epilepsies with seizures precipitated by specific modes of activation

Table II International Classification of Epilepsies and Epileptic Syndrome and Related Seizure Disorders (cont.)

Cryptogenic or Symptomatic

West syndrome

Lennox-Gastaut syndrome

Epilepsy with myoclonic-astatic seizures

Epilepsy with myoclonic seizures

Symptomatic

Nonspecific etiology

Early myoclonic encephalopathy

Early infantile epileptic encephalopathy with suppression burst

Other symptomatic generalized epilepsies

Specific syndromes

Epileptic seizures complicating other disease status

Epilepsies and syndromes undetermined whether focal or generalized

With both generalized and focal seizures

Neonatal seizures

Severe myoclonic epilepsy of infancy

Epilepsy with continuous spike waves during slow-wave sleep

Acquired epileptic epilepsies

Other undetermined epilepsies

Without unequivocal generalized or focal feathers

Special syndromes

Situation-related seizures

Febrile convulsion

Isolated seizures or isolated status epilepticus

Seizures occurring only with acute metabolic or toxic events

From the Commision on Classification and Terminology of the International League Against Epilepsy, 1989

Table III Common idiopathic epilepsies

Diagnosis	Demographics	Clinical features	EEG	Prognosis
Childhood absence epilepsy (generalised)	Onset age 3–10 years. Female >> male. 0.01–0.1% of children	Brief vacant spells occur many times per day and may present with school failure. Tonic-clonic seizures uncommon	Generalised spike and wave at 3 Hz. Nearly always triggered by hyperventilation. Photosensitivity uncommon	Remission in 75% by age 30
Juvenile absence epilepsy (generalised)	Onset age 7–16 years Female > male 0.005–0.03% of children	Brief vacant spells occur infrequently. Tonic-clonic seizures in 90%	Generalised polyspike and wave at 3–4 Hz. Nearly always triggered by hyperventilation. Photosensitivity in 20%	Usually requires lifelong treatment
Juvenile myoclonic epilepsy (generalised)	Onset 7–30 years. Female 3:2 male. 3–12% of all epilepsy	Myoclonic jerks and tonic-clonic seizures in nearly all patients. Absences in 20%	Generalised polyspike and wave. Photosensitivity in 33%	Usually requires lifelong treatment
Epilepsy with tonic-clonic seizures on waking (generalised)	Onset age 6–30 years. Uncommon	Tonic-clonic seizures, sometimes preceded by myoclonic jerks	Generalised spike and wave in 40%	Usually requires lifelong treatment
Eyelid myoclonias with absences (generalised)	Onset age 3–10 years. Nearly all female. Some familial cases	Hundreds of seizures daily starting with 4–6 Hz clonic movements of eyes and eyelids. Tonic-clonic seizures usually develop later	Generalised spike and wave at 3–6 Hz. Extreme photosensitivity at onset in nearly all cases	Usually requires lifelong treatment
Benign epilepsy with centrotemporal spikes (focal)	Onset age 1–15 years. Male > female. 10–15% of childhood epilepsy	Occasional nocturnal seizures start with drooling and twitching one side of face and spread to hemiclonic or tonic-clonic seizures	Centrotemporal spikes usually occur in sleep and may switch sides	Usually remits after 3 years. Treatment often not required
Young onset benign occipital epilepsy (focal)	Median onset 5 years. Male = female. 13% of benign focal epilepsy	Infrequent seizures last up to 30 minutes. Headache and tonic deviation of eyes associated with vomiting may evolve to tonic-clonic seizures	Occipital paroxysms occur on eye closure	Median seizure number is 3 before remission
Older onset benign occipital epilepsy (focal)	Age of onset 3–16 years. Male = female. 5% of benign focal epilepsy	Seizures several times per day or week start with visual hallucinations or ictal blindness	Occipital paroxysms are blocked by visual fixation	Usually remits in late teens

Incidence(12)

The overall incidence of childhood epilepsy from birth to 16 years is approximately 40 in 100,000 children per year. The incidence in the first year of life is about 120 in 100,000. Between 1 and 10 year of age, the incidence plateaus at 40 to 50 in 100,000 and then drops further in the teenage years to about 20 in 100,000. The details of incidence by year of life from the Nova Scotia childhood epilepsy study study are illustrated in Figure I. Hauser and

Hesdorffer estimate that about 1% of children will have at least one afebrile seizure by age 14 years and 0.4% to 0.8% will have epilepsy by age 11 years.

Seizure types vary in incidence. Generalized tonic-clonic or various types of partial seizures dominate about 75% of childhood epilepsy syndromes. Absence epilepsies account for approximately 15%, and other generallized epilepsies account for only 10%. This latter group consists of the majority of the catastrophic epilepsy syndromes, including West syndrome, Lennox-Gastaut syndrome, and severe myoclonic epilepsy of infancy.

Prevalence data for seizure or epilepsy type are not easily collated because of varying definitions of active epilepsy. When active epilepsy was 4.3 to 9.3 in 1000. Because some epilepsies are much less likely to remit, they contribute more to prevalence of the disorder than its incidence. Therefore the relative prevalence of symptomatic generalized implication of these observations in that physicians who focus on newly diagnosed children with epilepsy encounter a predominance of benign disorders. Those primarily treating chronic cases will note a higher proportion of more malignant seizure disorders.
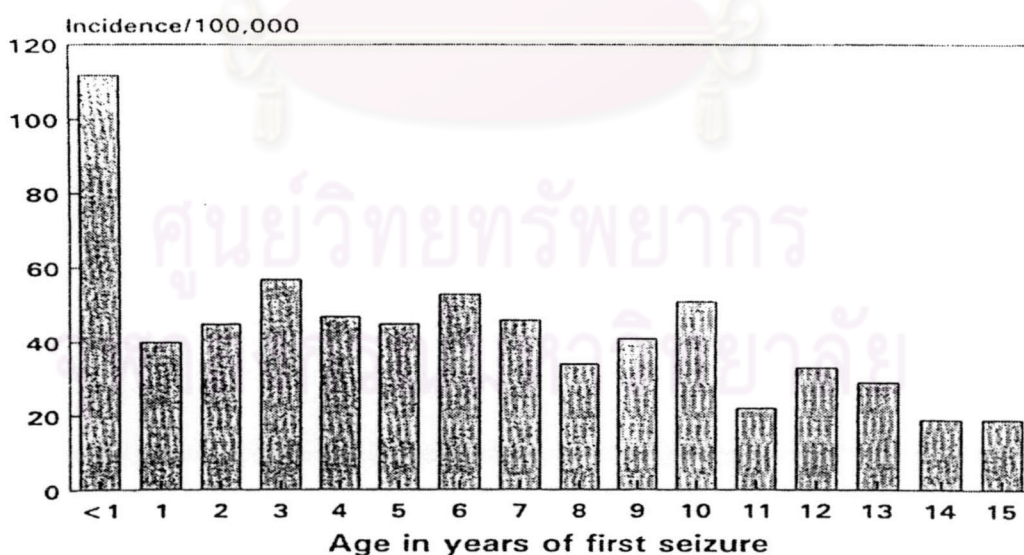

Figure I Incidence of epilepsy by age of onset

(Reprinted from Camfield et al. 1996)

Differential diagnosis(12)

The diagnosis of epilepsy in based almost exclusively on a clinical history of two or more unprovoked seizures. Parents vary in their capacity to describe these frightening events, and physicians vary in their ability to ask good questions. Therefore some children are misdiagnosed. A Dutch group of neurologists shared case descriptions of childhood seizure disorders and were able to agree about the majority of diagnoses of epilepsy. However, even experts sometimes disagree. Reflex anoxic seizures associated with pallid or vasodepressor syncope or with cyanotic breath-holding are particularly likely to be misinterpreted.

The electroencephalogram (EEG) cannot be used to make the diagnosis of epilepsy unless an actual seizure is recorded. Since most children with epilepsy have infrequent seizures, it is unusual to record a seizure on routine EEG. A small percentage of normal children will have epileptiform activity on EEG but never have a seizure. It is unclear why many children with chronic epilepsy never demonstrate epileptiform discharge on interictal EEG—the number may be as high as 40%. That percentage does not diminish the value of the EEG in syndrome classification; however, the EEG may change significantly over time and reveal conflicting findings. Therefore the interictal EEG is probably best viewed as offering broad hints about the specific diagnosis, but it must be interpreted in the clinical context.

Likewise, the diagnosis of epilepsy cannot be based on brain-imaging studies studies. The presence of an anomaly on MRI, for example, increases the possibility of epilepsy and, depending on the nature of the abnormality, increases the likelihood of a specific syndrome. For example, lesions typical of tuberous sclerosis in the first year of life increase the risk that a child will have West syndrome. Only the clinical history or video EEG can turn a "hunch" into a definite diagnosis.

The epilepsies are syndrome classified according to a combination of characteristic including clinical seizure type, EEG, and aetiology (Figure II)(13)
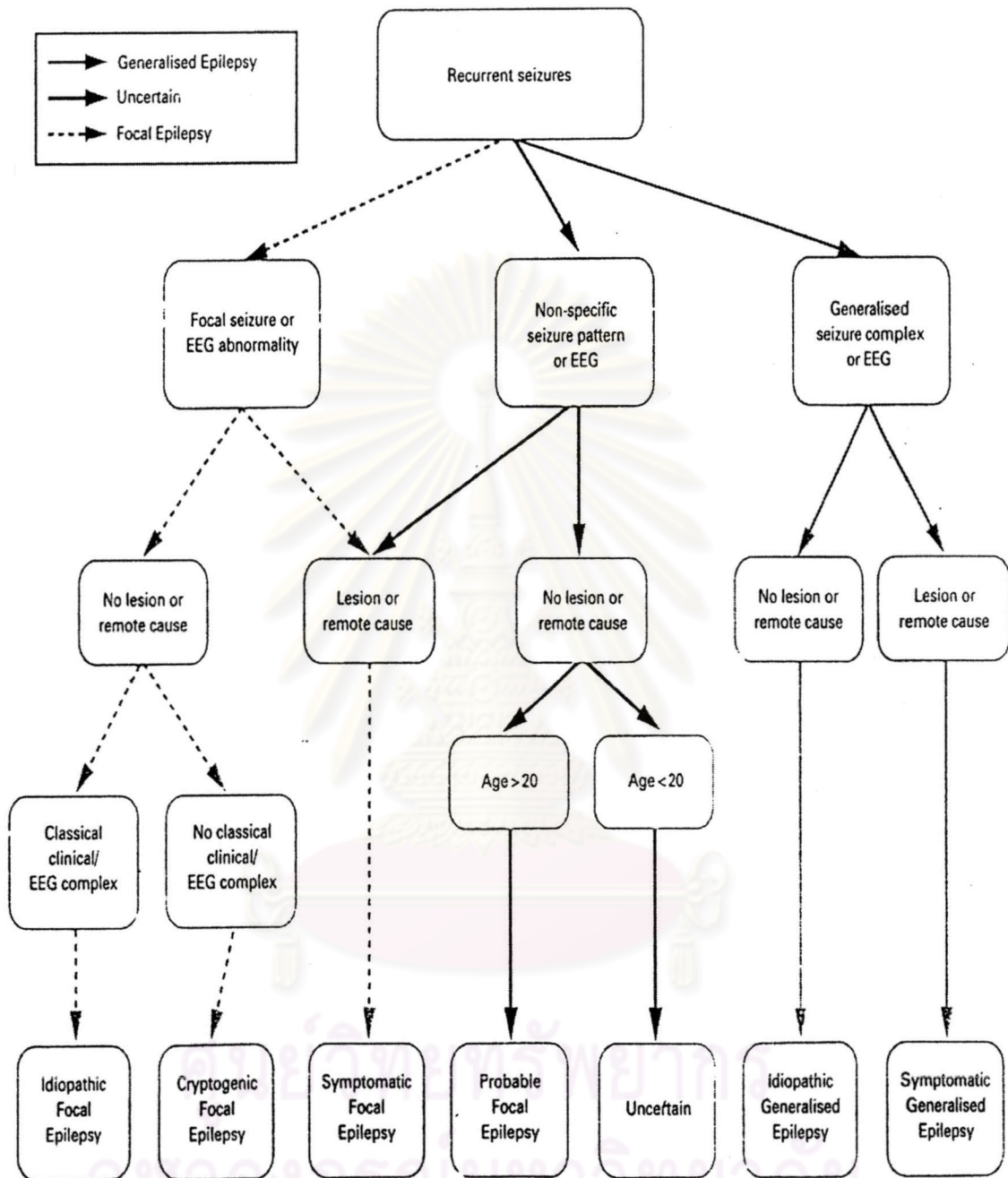
Figure II Simplified scheme for diagnosing epilepsy, excluding acute symptomatic seizure

Treatment

Desired outcome

The ultimate goal of treatment for epilepsy is no seizures and no side effects with an optimal quality of life. The best quality of life is associated with a seizure-free state. Often, however, a balance between efficacy and side effects must be reached, because with the older antiepileptic drugs (AEDs) used as monotherapy, fewer than 50% of patients become seizure free.

Because therapy is extended for many years (often a life-time), chronic side effects must be considered. If the patient is overly sedated or develops other significant side effects, some seizure control may have to be sacrificed to improved functioning. The patient should be involved in deciding what balance between frequency of seizures and the occurrence of side effects is most appropriate. The newer ADEs offer alternatives for balancing seizure frequency and drug side effects.

Providing optimal quality of life goes beyond balancing seizures and side effects. It involves assessing all the concerns of a patient with epilepsy. For example, patients with epilepsy are concerned about driving, their future, forming relationships, housing, social isolation, social stigma, and so on. Despite public awareness programs, there are still many misconceptions about epilepsy. These misconceptions often liken epilepsy to mental retardation, possession by demons, or punishment by God. Patients may be encouraged to contact or join the Epilepsy Foundation of America (1-800-EFA-1000) or other support groups that encourage patients with epilepsy to lead normal lives. Knowledge about epilepsy has been correlated with an improved quality of life. (6,12,14)

Prior to 1990, the medical treatment of a patient with epilepsy was accomplished by administering one or a combination of the available antiepileptic drugs (AEDs). The patient was started on a drug thought to be among the most effective for the seizure type and epilepsy syndrome. For partial seizures, carbamazepine, phenytoin, phenobarbital, primidone, and valproate most commonly were used, and patients with primary generalized seizures,

received valproate. For the treatment of absences, ethosuximide or valproate was usually prescribed. Initial drug choice frequently depended on the acute nature of beginning seizure therapy.(15)

Antiepileptic Drug Therapy in Children

Rational management of drug therapy in children require an understanding of pharmacokinetics, and toxicology. Pharmacokinetics is the study of drug absorption, distribution, metabolism, and elimination; or what the body does to a drug. Pharmacodynamics is the study of a drug's biochemical and physiologic effects or what the drug does to the body. Children, much more than adults, have widely varying abilities to absorb, distribute, metabolize, and eliminate drugs, Evidence also exists that antiepileptic drug (AED) pharmacodynamics in children differ from those in adults. Application of basic pharmacokinetic and pharmacodynamic principles to AED therapy facilitates the attainment and maintenance of targeted serum concentrations, clinical response, control of drug interactions, and optimization of clinical response. (16,17)

Starting Medication Treatment

There is little justification for being daily medication after a child's first unprovoked seizure, since 60% will never have another attack. Also, population-based studies have found that medication prescription after the first seizure does not alter the recurrence rate, probably on account of poor compliance with medication taking. A large, open-label, randomized trial of medication versus no medication after a first seizure in 397 children and adults demonstrated a significant reduction in recurrences for those on medication over a 2-year treatment period *[First Seizure Trial Group, 1993]*. The risk of recurrence without treatment was 51% by 24 months, but there were still relapses in 25% of those randomized to medication (i.e., 2.8 times higher; 95% confidence interval [CI], 1.9 to 4.2). It has become common practice to prescribe medication after a second seizure. There is no evidence that the prescription of medication alters the long-term outlook of childhood epilepsy.

There is convincing information that delaying antiepileptic drug treatment until the child has had up to ten seizures does not alter the ease of seizure control or the long-term remission rate. In other words, if a child has few seizures, there is no evidence that each seizure facilitates the next. The main reasons to treat children with antiepileptic drugs are the avoidance of bodily injury from seizures and improvement in psychosocial function. Neither of these issues has been extensively investigated. In a group of 59 children with generalized absence seizures followed over 15 years, the previous report noted that 16 had a serious physical injury as the result of a seizure. Hodgman studied 25 adolescents with grand mal epilepsy and noted that those with poorer seizure control were better to communicate about seizures and had a better self-image. The "hidden handicap" for children with controlled seizures may have important effects on social adjustment. (12) The drug treatment of first choice depend on the type of epilepsy (Table IV) as well as the interface between drug specific adverse effects and patient preferences. (6)

Table IV Drugs of choice for specific seizure disorder

Seizure type	Commonly used initial drugs	Alternative Drugs
Partial	Carbamazepine Phenytoin Valproic acid	Felbamate Gabapentin Lamotrigine Phenobarbital Tiagabine Topiramate Vigabatrin
Tonic-clonic	Phenytoin Valproic acid Carbamazepine	Phenobarbital Lamotrigine
Absence	Ethosuximide Valproic acid	Clonazepam Acetozolamide

Bilateral massive
   epileptic myoclonus,
   atonic, infantile spasms
	Clonazepam
	ACTH
		Phenytoin
		Phenobarbital
		Benzodiazepines
		Acetazolamide
		Felbamate
		Topiramate
		Vigabatrin

Juvenile Myoclonic Epilepsy(JME)	Valproic acid	lamotrigine

When medication is started the majority of children will still have more seizures. Only about 20% will have "smooth sailing epilepsy," meaning that they start medication, become immediately seizure free, and later are able to successfully discontinue medication without ever having another seizure. Furthermore, only 50% of children will continue to receive the same medication a year after starting treatment (Canadain Childhood Epilepsy Study Group, 1993). Therefore the decision to start medication is often not the end of the seizure problem. (12) Few guidelines or treatment protocols have been published. Figure III is a suggested algorithm for a general approach to the treatment of epilepsy. (6)
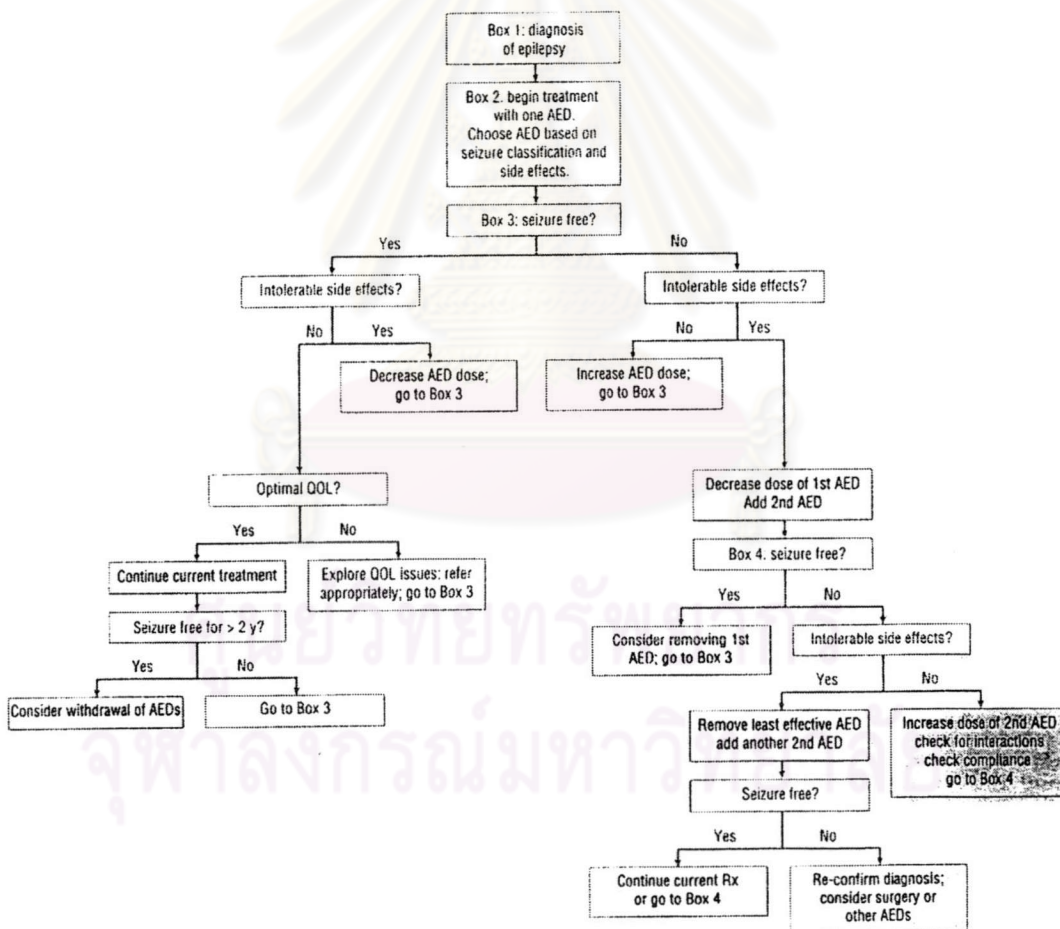

Figure III Algorithm for treatment of epilepsy

Clinical and Laboratory Monitoring During Therapy (16)

Clinical Monitoring of Therapeutic Efficacy

The clinical assessment of patients on anticonvulsant therapy is of paramount important. The clinician needs to assess the effectiveness in therapy with regard to seizure control. It is also necessary to determine if there are adverse effects and whether these are tolerable. A satisfactory clinical response to AED therapy would include a substantial reduction or elimination of seizures and/or a reduction of adverse effects. Total elimination of seizures with no adverse effects of medication would be ideal; however, the response to therapy is usually not that obvious.

It is necessary to be at steady state to determine if a medication has been given an adequate clinical trial. The time to achieve steady state varies considerably from drug to drug depending on the individual's half-life, but in every case 5-half-lives must elapse to attain a new steady state.

Clinical Monitoring of Adverse Effects

Clinical assessment is of primary importance in assessing adverse response. Factors such as steady-state conditions and effects of drug interactions are equally applicable in the clinical assessment of adverse effects.

Pharmacokinetic Principles and Monitoring of Anticonvulsant Concentrations

AED pharmacokinetics differ qualitatively and quantitatively between children and adults. Children, particularly neonates, have greater variability than adults in their ability to absorb and eliminate AEDs. There are many potential sources of variability including drug formulation, behavior (compliance, diet, substance abuse), environment, and physiology. Physiologic variability may be correlated with the health of the subject, but also with factors such as pregnancy, gender, age and maturation. In the management of pediatric seizures, the concern is with the effects of age and maturation on the pharmacokinetic profile; however behavior, especially in adolescence, can also be major determinant influencing clinical decisions. Other than age-related

differences, drug-specific pharmacokinetics such as saturable metabolism, protein binding, and enzyme induction are similar for children and adults.

The ability to measure plasma levels of antiepleptic drugs has been a major advance in the medical management of epilepsy. The influence of periodic monitoring of blood levels on therapy has reduced the number of therapeutic failures by 50%. Anticonvulsant levels are generally obtained after each change of dosage. Drug levels are generally related to dose administratered except for drugs with nonlinear kinetics, such as phenytoin and carbamazepine. Unless there is some overriding clinical decision to do otherwise (i.e., development of acute toxicity or deteriorating seizure control), it is reasonable and economical to wait until steady-state is obtained before drawing blood levels. The addition, reduction or discontinuation of other antiepileptic medication during AED therapy can have a profound effect on concomitant antiepileptic drugs. Therefore, obtaining repeat drug concentrations when a second medication is added or discontinued is often useful. In children, more frequent AED levels may be especially helpful because there is more patients-to-patient variation and because children are undergoing rapid change in metabolism and weight. Change formulation may also produce changes in the AED concentrations. Therefore, plasma AED levels should be monitored more closely at times of formulation changes so that the desired AED concentrations are maintained. Rechecking AED levels when clinical problems (e.q., interpretation of possible toxicity in the presence of other nonspecific illness, loss of seizure control) are present is also useful. The determination of blood levels in this circumstances enables the physician to determine if problems with compliance, absorption, or drug interaction exist.

What to Measure

Newer technologies are improving the ease and lowering the cost of making unbound determinations; however, most of laboratories routinely perform only total drug concentrations. However, situations exist in which unbound drug concentrations might be especially helpful. Some patients develop clinical toxicity at either relatively low dose or low total concentrations.

A higher than expected unbound could explain the basis of the clinical toxicity. These circumstances particularly arise during multiple drug therapy when a second may displace the first from protein binding sites or with illness that results in lower plasma protein levels. The percentage of unbound valproate increases with higher drug concentrations and with co-medication. When the bound fraction is doubled, the valproic acid free fraction may be eight times higher.

The measurement of AED metabolites can also be useful. Many AED metabolites are clinically active and contribute both to clinical response and toxicity. A noteworthy example children exhibit a higher carbamazepine/carbamazepine-10,11 epoxide ratio than adults; therefore, although higher doses are needed to achieve carbamazepine concentrations in the therapeutic range, their carbamazepine-10,11 epoxide plasma levels may be higher than expected.

Interpretation of Drug levels

Numerous factors should be considered in interpretation of drug levels. Drugs that have rapid absorption and clearance show wide fluctuation between dosing intervals. For example, valproic acid syrup, especially when given to a child with enzyme-inducing co-medication, is rapidly absorbed and eliminated and may cause a twofold fluctuation during a dosing interval. Recording the time of the blood sample with regard to the last dose is frequently necessary to determine whether a trough, peak, or mid specimen dose is obtained. Unexpectedly high or low values may also arise from overzealous administration or poor compliance.

Laboratory monitoring other than AED level

Liver function tests, serum amylase levels, CBC, and platelet counts should be performed prior to treatment and at frequent intervals thereafter. A rise in the hepatic transaminase levels without associated symptoms or other biochemical abnormalities may be successfully manages by a reduction in dosage. The drug should be discontinued if the patient develops sign of liver failure, pancreatitis, or biochemical abnormalities other than transient hepatic transaminase elevation.

Long-Term Remission

For many children, epilepsy is transient, and with maturation the problem seems to vanish. At the time of diagnosis, it is possible to predict that at least 50% of children will outgrow their disorder and be able to discontinue medication. The longer the follow up, the higher the proportion with remission. In Rochester, Minnesota, 115 children with epilepsy beginning before age 10 years were followed through the Mayo Clinic record linkage system. Ten years later, 75% had been seizure free for at least 5 years and 51% no longer received medication. At the end of a remarkable 30 year follow up study of children with epilepsy from a population-based sample in Turku, Finland, Sillanpaa noted that 76% of survivors had been seizure free for at least 3 years.

Across the majority of studies, factors that predict which children will outgrow their epilepsy have included normal intelligence, normal neurologic examination, relatively small numbers of seizures at diagnosis (presumably a proxy measure for complex partial seizures), age of the first seizure less than about 12 years, and absence of a remote symptomatic etiology. In an 8-year follow-up study of a population-based study of 504 children with epilepsy from Nova Scotia a predictive scoring system was developed; it is outlined in Table V.(12) Those with a good prognosis had an 80% chance of remission (seizure free and no longer receiving medication). For those with one or more of these adverse factors, the chance of remission was less but still about 40%.

Table V Scoring system (at time of diagnosis)

for remission in childhood epilepsy

Variable	Score*
Age of first seizure (months)	
<12	99
12 to 144	142
>144	0
Intelligence	
Normal	111
Retardation	0
Previous neonatal seizures	
No	218
Yes	0
Number of seizures before starting medication	
1 or 2	72
3 to 20	123
>20	0

Add the scores from this column. If the total score is greater than 495, the child is predicted to have remission of epilepsy. Adapted from Sillanpaa M et al., Arch Neuro 1995;52:589.

Stopping Medication

About 70% of children with epilepsy who have become seizure free for 1 to 2 years can successfully stop medication treatment. The rate of success is no greater if medication is continued for up to 5 years seizure free. Factor which have been proposed as predictors of seizure relapse are depicted in Table VI. Factors that predict successful discontinuation of medication include generalized seizures, age of onset before age 10 to 20 years, normal neurologic examination, and, in some studies, resolution of interictal EEG spike discharges. (16,17) Children with no adverse factors may have an 80% to 90% success rate. Each factor has an additive effect and those with all of the adverse factors may have only a 10% to 20% success rate.

If an initial discontinuation trial is unsuccessful, medication is usually restarted. About 50% of children will again become seizure free for sufficient time to discontinue a second time with a 70% success rate. The remission rate in

juvenile myoclonic epilepsy is so low that further attempts to discontinue medication after an initial failure are probably not warranted.

A Scandinavian study randomized 207 children at the time of diagnosis of epilepsy to receive either 1 year of treatment or 3 years of treatment. If the child was seizure free for the last 6 months of study, medication was discontinued. This meant that some of the children in the 1-year treatment group had only been seizure free for 6 months before medication was stopped. The success rate in those in the short treatment group was significantly less than the 3-year group (53% versus 71%). Nonetheless, for a substantial number of children, epilepsy was a short-lived disorder requiring only short-term medication usage. Children with hemiparetic cerebral palsy were significantly more likely to experience relapse (61.5%) than those with spastic diplegia.(16) Further studies will likely identify some children who do not require any medication treatment.

Table VI Factors proposed to be associated with an increased risk of seizure relapse after treatment withdrawal

Variable
Type of seizures and epilepsy (see text)
Age of patient[a]
Age at onset of seizures[a]
Prolonged duration of epilepsy or high number of seizures before control
Known aetiology of seizures and associated neurological handicaps
Abnormal activity in the EEG
History of afebrile and atypical febrile seizures
History of status epilepticus
Short duration of seizure-free period
Polytherapy at time of discontinuation
Particular drug withdrawn
Fast rate of drug withdrawal
[a] Role of age is controversial.

Valproic acid

1. Structure

Valproic acid is a branched-chain fatty acid (Figure IV) and differs structurally from other antiepileptic drugs due to its lack of a nitrogen molecule or a heterocyclic moiety. The drug is available in several forms, including the parent compound, its sodium salt, its amide derivative, and a combination of the parent compound and its sodium salt in a 1:1 molar ratio. In addition, valproic acid and sodium valproate are available in capsule, tablet, enteric-coated tablet, sprinkle, liquid, intravenous, suppository and controlled-release formulations. Since the drug is available in a variety of salts and formulations throughout the world, the term "valproic acid" is use throughout the present review.(4,5)
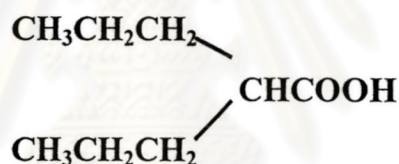
$$CH_3CH_2CH_2 \diagdown$$
$$_{\diagup} CHCOOH$$
$$CH_3CH_2CH_2 \diagup$$

Figure IV Structural-formula of valproic acid

2. Chemistry and stability(4)

Valproic acid, valproate sodium, and divalproex sodium are carbolic acid-derivative anticonvulsants. Valproic acid is structurally unrelated to other commercial available anticonvulsants; it lacks nitrogen and/or an aromatic moiety found in most anticonvulsants. Divalproex sodium is a stable coordination compound consisting of valproic acid and valproate sodium in a 1:1 molar ratio and is formed during partial neutralization of valproic acid with sodium hydroxide. Divalproex sodium is a prodrug of valproate, dissociating into valproate in the gastrointestinal tract.

Valproic acid

Valproic acid occurs as a colorless to pale yellow, slightly viscous, clear liquid with a characteristic odor and is slightly soluble in water and freely soluble in alcohol. Valproic acid has a pKa of 4.8. USP recommends that valproic acid capsules be stored in tight containers at 15-30°C; however, the manufacturer of Depakene recommends that the capsules be stored in tight containers at 15-25 °C.

Valprote sodium

Valproate sodium occurs as a white, crystalline, very hygroscopic powder with a saline taste and is very soluble in water and in alcohol. Valproate sodium oral solution has a pH of 7-8. Valproate sodium oral solution should be stored in tight containers at a temperature less than 40 °C, preferably between 15-30 C; freezing should be avoid.

Diproex sodium

Diproex sodium occurs as a white powder with a characteristic odor and is insoluble in water and very soluble in alcohol. Divalproex sodium delayed-release tablets should be stored in tight, light-resistant containers at a temperature less than 30°C; divalproex sodium capsules containing coated particles should be stored at a temperature less than 25 °C.

3. Pharmacology(3,4)

The mechanism of action of valproic acid is not known. Effects of the drug may related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA). Animal studies have shown that valproic acid inhibits GABA tranferase and succinic aldehyde dehydrogenase, enzymes which are important for GABA catabolism. Results of one study indicate the drug inhibits neuronal activity by increasing potassium conductance. In animals, valproic acid protects against seizures induced by electrical stimulation as well as those induced by pentylenetetrazol.

4. Pharmacokinetic Properties(4,7,16)

Absorption. Valproic acid is rapidly absorbed when given orally. The absorption rate of valproic acid depends on the formulation used. Absorption is fastest from the valproic acid syrup followed by the gelatin capsule, the enteric-coated tablet, and the sprinkle formulations. The time to peak concentration with syrup and gelatin capsule is between 1 to 3 hours. The enteric-coated tablet and the sprinkle formulations were formulated to delay absorption and to minimize the gastrointestinal irritation associated with valproic acid. Absorption from the enteric coated tablet dose not begin for 2 to 4 hours after administration, but once absorption begins valproic acid reaches the systemic circulation very quickly at a rate similar to that of rapid release formulations. Peak concentrations with the enteric-coated tablets are not seen for 4 to 8 hours. The enteric-coated tablet is not a sustained-release formulation. Recently a circadian effect on the absorption of valproic acid from enteric-coated tablets has been reported. Although not designed to be a controlled release formulation, the sprinkle formulation results in a prolonged absorption that approaches a zero order input. The absorption of valproic acid given as a rectal solution, prepared by mixing the syrup and water in a 1:1 ratio, is comparable to that of oral formulations; however, the maximum concentration is lower and the time to peak is longer. The rectal route may be used for maintenance therapy, but the slow absorption precludes its use in emergency situations. After absorption begins the pharmacokinetics of all of the valproic acid formulations are similar.

The bioavailability of all of the valproic acid formations is believed to be about 100 %. Food may delay the rate of drug absorption but dose not affect the extent of absorption. There is no first metabolism of valproic acid.

Distribution More than 90 % of valproic acid is ionized at physiologic pH. Therefore, the drug is highly bound to plasma protein relative to tissue protein. The volume of distribution of the unbound drug is higher than the volume of distribution for the total drug. At concentrations up to 80 to 100 g/mL, valproic acid is 90 to 95 % bound to plasma proteins, mainly albumin. At higher concentrations, however, the protein binding saturates and the free

fraction increases is a percentage that is disproportionate to the amount of dosage increase. The protein binding may be altered in disease states in which the synthesis of albumin may be altered, for example, cirrhosis, chronic renal failure, and extremes of age. The diurnal fluctuation seen with valproic acid concentrations is greater with the unbound than with the total concentration. Free fatty acids may compete with valproic acid for binding sites on the albumin molecule.

Valproic acid enters the brain and cerebrospinal fluid (CSF) very rapidly. An equilibrium develops between the CSF and plasma concentrations of valproic acid, and a ratio of about 0.1 to 0.15 is established for the total valproic acid concentration. CSF concentrations have been reported to equal the serum unbound concentrations. Valproic acid also distributes to a variety of other tissues that include the liver, kidney, breast milk, growing bones, intestines, and the developing fetus. Some valproic acid may bind to red blood cells. When given intravenously, valproic acid seems to follow a two-compartment model.

Metabolism and Elimination. Valproic acid is a low extraction drug and is extensively metabolized by the liver. Only 3 to 7% is excreted in the urine as unchanged drug. It is the unbound fraction that is metabolized. Therefore, when protein binding saturates and there is an increase in the percentage of free drug, the metabolism of valproic acid increases. Thus, there is an increase in clearance at higher serum concentrations. With an increase in clearance, the concentration of total drug increases less than the percentage increase in dose. There is significant intersubject variability in the metabolism of valproic acid. The average half-life of valproic acid has been reported to be 12 to 16 hours in adult volunteers; however, the half-life may be affected by the presence of other enzyme-inducing of inhibiting drugs and is highly variable in a patient population.

Valproic acid may be metabolized by conjugation, beta-oxidation and alpha hydroxylation. More than 10 metabolites have been identified. Some of these metabolites may have antiepileptic activity, and one of these, 4-en-valproic acid, has been associated with valproic acid-induced hepatotoxicity.

The 4-en-valproic acid metabolite may reflect an abnormal pathway that is used in the presence of other drugs of congenital abnormalities.

The elimination half-life of valproic acid is short. In the first few weeks after birth, haft-life range from 17 to 40 hours but rapidly declines from 3 to 20 hours in infants and young children. Evidence suggests that the full antiepileptic effect of valproic acid occurs days to week after reaching steady-state and this effect continues for some time after the drug is discontinued. The lingering effect may be partly the result of its inhibitory effect on the enzymes responsible for the degradation of gamma-aminobutyric acid or to the accumulation of 2-ene-valproic acid. This prolonged duration has prompted some to propose single daily dosing, however, there are other proposed mechanisms of action in which seizure control is related to plasma valproic acid concentrations. (16) Renal elimination dose not contribute significantly to the clearance of valproic acid.

Linear phamacokinetics (or dosage-dependent clearance) at steady state has been reported, although increased valproic acid clearance at higher dosages (non-linear pharmacokinetics) has also been observed. While dosage changes are usually accompanied by proportional changes in plasma drug concentrations, the linearity of valproic acid phamacokinetics may be disrupted when drug binding to plasma proteins is saturated (at higher dosages), resulting in an increased valproic acid clearance (13,16)(Figure V).

(A) Nonlinear pharmacokinetics (Michaelis-Menten type) clearance decreases with increasing dose
PHT

(B) Linear pharmacokinetics clearance remains the same with increasing dose
PB, FBM, VGB, TGB, TPM, VPA$_{unbound}$

(C) Nonlinear pharmacokinetics clearance increases with dose
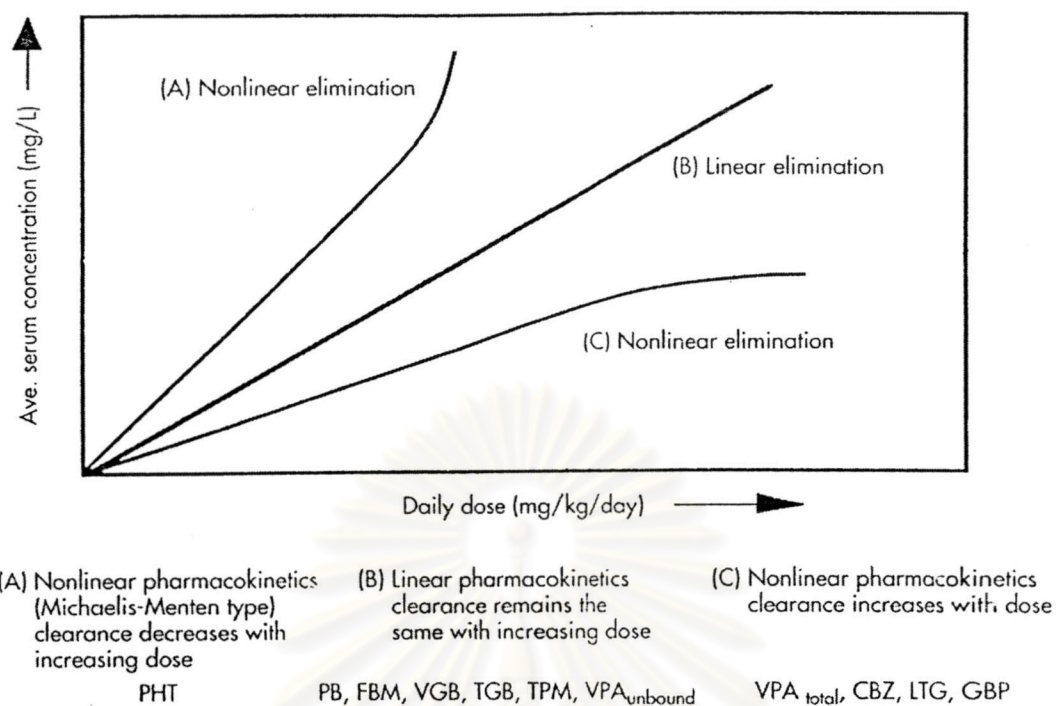VPA $_{total}$, CBZ, LTG, GBP

Figure V Effect of dose on elimination kinetics

Effects of Age

Neonates, Infants and Children

In neonates, $t_{1/2}$, Vd and the percentage of unbound valproic acid are increased compared with those infants or children. Mean $t_{1/2}$ varied considerably, and ranged from 30 to 60 hours in untreated neonates born to epileptic mothers, and from 17 to 40 hours in neonates treated with valproic acid. There was values decrease in the first few weeks of life, so that t1/2 values for infants approach those of adults. Factors such as age, total plasma drug concentration, and level of albumin and fatty acids can influence drug binding to plasma proteins. In a study of infants with epilepsy (mean age 10.7 months), the percentage of unbound valproic acid increased with total plasma drug concentration. Compared with adults, higher plasma clearance and lower t1/2 values were observed in children aged 2 to 10 years with epilepsy receiving valproic acid as monotherapy or with concurrent antiepileptic drugs. Valproic acid clearance decreased with increasing paediatric age; pharmacokinetic parameters in children aged ≥10 years were similar to those reported in adults.

The Elderly

The pharmacokinetics of valproic acid in non-epileptic elderly patients and volunteers has been compared with those of young, healthy volunteers. Following intravenous administration of valproic acid 400 mg to 6 elderly patients and 7 young adult volunteers, a 2-fold prolongation of $t_{1/2}$ with and increase in Vd was observed in the elderly patients; however, plasma clearance did not differ between the 2 groups. Subsequent studies revealed that pharmacokinetic parameters in the elderly based on total plasma valproic acid concentrations did not differ significantly from those observed in younger volunteers. The previous study observed that steady state clearance of unbound drug in the morning (0.064 vs 0.106 L/h/kg) and evening (0.075 vs 0.123 L/h/kg) was significantly reduced in elderly (60 to 88 years old) compared with young volunteers (22 to 25 years old). In addition, unbound plasma valproic acid concentrations at steady state were about 67% higher in the elderly patients due to a reduction in drug binding to plasma proteins. Total plasma drug concentrations remained the same, indicating reduced liver metabolism.

5. Clinical Efficacy

5.1 Clinical Effect in Epilepsy(4)

There are multiple levels of diagnosis in every patient with epileptic seizures. Epilepsy or epileptic syndromes can be classified by etiology, anatomical basis, EEG characteristics, patient age or seizure type.

Complete control of epileptic seizure activity is currently achieved in about 75% of patients; the remaining 25% have intractable seizures frequently unresponsive to polytherapy. It is this latter group in which new antiepileptic drugs are usually first tested using an add-on trial design, where the investigation agent is given in addition to the patient,s current antiepileptic regimen. This trial design is unethical and undesirable because of the potential of increased seizure frequency and status epilepticus with consequent neurological injury or death.

In the previous review of valproic acid in the journal, the drug had proven efficacy in reducing the incidence of both generalized and partial seizure in several clinical trials of add-on design. In spite of these encouraging results for the treatment of partial seizures, valproic acid was used primarily for the treatment of generalized seizures. Subsequently, clinical trials have supported long term (up to 5 years) use of valproic acid monotherapy, particularly for treatment of generalized (absence and tonic-clonic) seizures. In addition, when compared with other antiepileptic drugs (carbamazepine, phenytoin, ethosuximide, and phenobarbital), valproic acid demonstrated equivalent efficacy rates for the treatment of both generalized and partial seizures. Valproic acid monotherapy or polytherapy has also been effective in the treatment of children with generalized or partial seizures untreated or refractory to therapy with other antiepileptic drugs.

5.2 Efficacy in acute mania

Divalproex sodium is used in the treatment of manic episodes associated with bipolar disorder; valproic acid and valproate sodium also have been used. Because there are only minor differences in the pharmacokinetics of the formulations, and because all forms of the drug circulate in plasma as valproic acid, the term "valproic acid" will be used in the following discussion.

Valproic acid has been used as monotherapy or as part of combination therapy (e.g., with lithium, antidepressants, or carbamazepine) in the treatment of acute manic episodes. A manic episode is a distinct period of abnormally and persistently elevated, expensive, or irritable mood. Typical symptoms include pressure of speech, motor hyperactive, reduced need for sleep, flight of ideas, grandiosity, poor judgement, aggressiveness, and possible hostility. Efficacy of valproic acid in the treatment of manic episodes was established in short-term, placebo-controlled, parallel-group trials in patients hospitalized with bipolar disorder, manic (DSM-IIIR); response to therapy was assessed using objective rating scale such as the Young Mania Rating Scale (YMRS), and augmented Brief Psychiatric Rating Scale (BPRS-A), the Mania Rating Scale (MRS), and

the Global Assessment Scale (GAS). One study specifically enrolled patients who were intolerant of or unresponsive to previous lithium therapy. Up to 40% patients fail to response to or are intolerant of lithium therapy for manic episode; such patients may demonstrate a response to valproic acid, although response to valproic acid appear to be independent of prior response to lithium therapy. Valproic acid therapy appears to be about as effective lithium for treatment of manic episodes. Although the manufacturer states that safety and efficacy of long-term (i.e., longer than 3 weeks) valproic acid therapy have not been established in the treatment of manic episodes, valproic acid also has been used, alone or in combination therapy, for long-term of maintenance antimanic therapy. Antimanic efficacy has been maintained from several months to more than 10 years, and such long-term therapy appears to decrease the frequency and severity of bipolar episodes over extended periods of time; however, further study is required to establish the efficacy of valproic acid does not appear to be as affective for management of the depressive component of bipolar disorder; although some evidences suggests that long-term valproic acid therapy may be moderately effective in the prophylaxis of depressive episodes, its acute effects on depression appear o be limited. Some clinicians recommend that valproic acid therapy be used in patients with bipolar disorder or schizoaffective disorder, bipolar type, who have responded inadequately to or have been unable to tolerate treatment with lithium salts or other therapy (e.g., carbamazepine), particularly if the patient displays residual manic symptoms, or in the presence of rapid-cycling, dysphoric mania or hypomania, associated neurologic abnormalities, organic brain disorder.

5.3 Migraine prophylaxis

Divalproex sodium is used in the prophylaxis of migraine headache, with or without associated aura; valproic acid and sodium valproate also have been used. (18,19) Because there are only minor differences in the pharmacokinetics of the formulations, and because all forms of the drug circulate in plasma as valproic acid, the term "valproic acid" will be used I the following discussion.

Because valproic acid may pose a hazard to the, it should be considered for women of childbearing potential only after this risk has been discussed thoroughly with the patient, and weighed against the potential benefits of treatment.

Valproic acid was demonstrated to be effective in the prophylaxis of migraine headache in 2 randomized, double-blind, placebo-controlled trials in patients with at least a 6-month history of migraine, with or without associated aura. Patients also had to experience at least 2 migraine per month in the 3 months prior to enrollment in the studies; patients were exclude if they had cluster headaches. Although women of childbearing potential were excluded from one study because of the teratogenic properties of valproic acid, they were included in the other, provided that they were practicing and effective form of contraception. In both studies

5.4 Status epilepticus (SE)

Valproate, now available for intravenous administration as Depacon, has been used for the treatment of refractory SE in children and myoclonic SE. Valproate has also been used in SE in elderly, and appear to be safe, even in the presence of cardiovascular instability and hypotension. There was no significant change in blood pressure, pulse or the need for vasopressors in 13 patients with SE and hypotension given a loading dose of 14.7-32.7 mg/kg Depacon intravenous. However, there is a case report of severe hypotension in an 11-year-old child after treatment of SE with 30 mg/kg intravenous valproate.(20)

6. Adverse drug reaction(4,21)

Administration of valproic acid in conjunction other antiepileptic agents confounds interpretation of its tolerbility profile, as the relative contribution of each drug to the effects experienced is often difficult to assess. The following discussion relies mainly on the overview provided by Schmidt, who complied data from 16 trials in a total of 1140 patients, and any reviews of valproic acid-induced hepatotoxicity.

6.1 In Adults

6.1.1 General Adverse Effects

The majority of adverse effects observed in adults during treatment with valproic acid were mild to moderate in severity, appeared early in therapy and generally did not require dosage adjustment. In contrast to other antiepileptic drugs, the adverse effects associated with valproic acid therapy tend to be gastrointestinal, rather than neurological in nature. Early clinical trials reported incidences of gastrointestinal adverse effects (dyspepsia, heartburn, nausea, and anorexia) which varied from 6% to 45%. These disturbances typically occurred with initiation of therapy and their incidence has been reduced to 3 to 6% with the use of enteric-coated formulations.

Weight gain (mean 8 to 14 kg) has been frequency reported in clinical trials, with an incidence ranging from 8 to 59%. Increases in body weight have been associated with an increase in fatty tissue due to an elevated appetite, reduction of facultative thermogenesis and increased availability of long-chain fatty acids due to compititive valproic acid binding to serum albimin. This untoward weight gain can sometimes be controlled by reducing caloric in take.

Data comparing the clinical tolerability of valproic acid with ather antiepileptic drugs in adults are available from 3 clinical trials of monotherapy and a multicentre survey of 509 patients undergoing long term (>3 months) anticonvulsant monotherapy. In a large, double-blind trial of valproic acid versus carbamazepine in 480 patients, valproic acid was associated with a greater incidence of weight gain >5.5 kg (20 vs 8%, $P<0.001$), hair loss/change in texture (12 vs 6%, $P<0.02$), and tremor (45 vs 22%, $P<0.001$), although rash was more often associated with carbamazepine (11 vs 1%, $P<0.001$). In trial of 140 patients, 16 of 70 patients withdrew due to adverse effects from phenytoin (nystagmus, ataxia, tremor, diplopia, mental changes, rash, jaundice) compared with 9 of 70 patients withdrew from valproic acid (tremor, irritability, restlessness, alopecia).

4.1.2 Hepatic Effects

Transient elevations of liver enzyme activity (alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase) have been observed in approximately 11% of patients receiveing valproic acid. However, these elevations are generally dosage related, asymptomatic, and return to normal with reductions in dosage or discontinuation of therapy.

Conversely, fatal hepatotoxicity is rare, idiosyncratic, non-dosage-related adverse effect associated with antiepileptic drug therapy. Clinical symtomps such as nausea, vomiting, anorexia, malaise, edema, lethargy or a sudden and inexplicable recurrence of seizures often manifest before changes in liver function tests and appear to be more reliable indicators of valproic acid hepatotoxicity.

6.1.3 Neurological Effects

Valproic acid is generally associated with fewer neurological adverse effects than other antiepileptic drugs. Fine motor of the hands, resembling benign essential tremor, was observed in 1 to 5% of patients during valproic acid treatment. Drowsiness and ataxia were less common in pateints receiving valproic acid monotherapy (1.4%) compared with polytherapy (14.4%), due to increased plasma concentrations of other antiepileptic drugs, especially phenobarbital. Additional, valproic acid has minimal impairment on cognitive function and behavior compared whit phenytoin or phenobarbital.

6.1.4 Dermatological Effects

The incidence of dermatological effects (rashes, hirsutism) associated with valproic acid therapy is very low (1%), although the reported incidence of hair changes (hair loss, changes in texture/color) ranged from 1 to 11%. These transient effects generally occur during the first 6 months of therapy and resolve without any alteration in dosage of valproic acid.

6.1.5 Effects on Laboratory Parameters

A number of change in laboratory parameters have been described with valproic acid administration. Transient elevated blood ammonia levels were observed in about 21% in 102 patients receiving valproic acid monotherapy. Valproic acid therapy has also been associated with impaired carnitine and lipid metabolism. Important the impairment of carnitine metabolism and liver function by valproic acid dose not appear to be a clinical important phenomenon, especially in well nourished patients receiving monotherapy.

Transient, asymptom elevations in plasma amylase levels occur with valproic acid therapy. However, rare and sometimes fatal cases of acute haemorrhagic pancreatitis, associated with clinical symptoms of nausea/vomiting and acute abdominal pain have been reported. If clinical symptoms of severe thrombocytopenia or inhibition of platelet aggregation appear (spontaneous bruising, haematoma, epistaxis), the drug should be withdrawn pending further laboratory investigation. Platelet counts and coagulation tests are recommended before initiating therapy, at periodic intervals and prior to planned surgery.

6.1.6 Effects on the fetus

Increase incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to both treated and untreated mothers with epilepsy. Use of antiepileptic drugs during pregnancy is also associated with an increased risk of congenital malformations. Although the precise biochemical mechanism for the teratogenic effects of valproic acid and other antiepileptic drugs is unknown, studies suggest that altered folate metabolism and/or interference with folate metabolism by antiepileptic drugs may be partly responsive for the malformation observed. In additional folic acid supplementation and if possible, dosage reduction should be considered when the use of valproic acid during pregnancy cannot be avoided.

6.2 In Children

The tolerability profile of valproic acid treatment in children presented below is based on the results from 4 clinical trials of monotherapy and a comparative review of adverse effects in 492 paediatrics patients. In a noncomparative trial, 25 of 154 children (16%) who received valproic acid monotherapy experienced adverse effects although none required discontinuation of treatment. Drowsiness (n=10), gastrointestinal problems (8), hyperknesia (8), transitory hair loss(4) and weight gain(4) were the most commonly reported adverse effects. However, in another non-comparative trial, mild but troublesome adverse effects occurred in 65 of 100 children, including weight gain (n=44), gastrointestinal disturbance (20), lassitude (9), transient enuresis (7), hair loss(6) and aggressive behavior (4). These authors also noted that yearly weight velocity, which had originally been within normal limits, exceeded or reached the 98th percentile in 38 of 44 children during the year after valproic acid was initiated.

In comparative trial of monotherapy, withdraw rates were similar for children receiving valproic acid (2 of 49) or carbamazepine (2 of 54), and lower than those observed in patients receiving phenytoin (5 of 54) or phenobarbital (6 of 10). A high incidence of patient withdrawals due to behavioral problem (n=5) to drowsiness (n=1) resulted in discontinuation of the phenobarbital arm this trial.

Gastrointestinal adverse effects (nausea, abdominal pain, anorexia), increased appitite and weight gain were repoted more frequently with valproic acid (10 vs 18 reported) while neurological adverse effects (somnolence, fatigue, dizziness, headache, insomnia) were reported more frequently with carbamazepine (60 vs 24 reports) in long term, multicenter trial comparing these agents in 260 children with epilepsy (Verity et al. 1994). Similar numbers of patients receiving valproic acid (n=18) or carbamazepine (n=15) withdrew from this trial due to adverse effects.

In a study of 392 paediatric outpatients who received long term (mean 2 years) monotherapy with phenobarbital (n=99), primidone (85), phenytoin (63), carbamazepine(35) or valproic acid(110), adverse effects occurred in 50% of all patients, necessitating treatment change in 18% and drug withdrawal in 7%. While the number of patients experiencing behavioural (n=19) and neurological (1) adverse effects were comparatively lower with valproic acid, digestive (31) adverse effect were most commonly associated with this agent (Figure VI). Of note, high rates of polyuria, polydipsia, and enuresis were reported in 9,7, and 4 patients, respectively, receiving valproic acid ad appeared to be related to higher plasma drug concentrations than those observed in patients experiencing no genitourinary adverse effects. Patient withdrawal rates due to adverse effects were broadly similar for valproic acid (8%), phenytoin(10%), primidone(8%), phenobarbital(4%), and carbamazepine (3%).
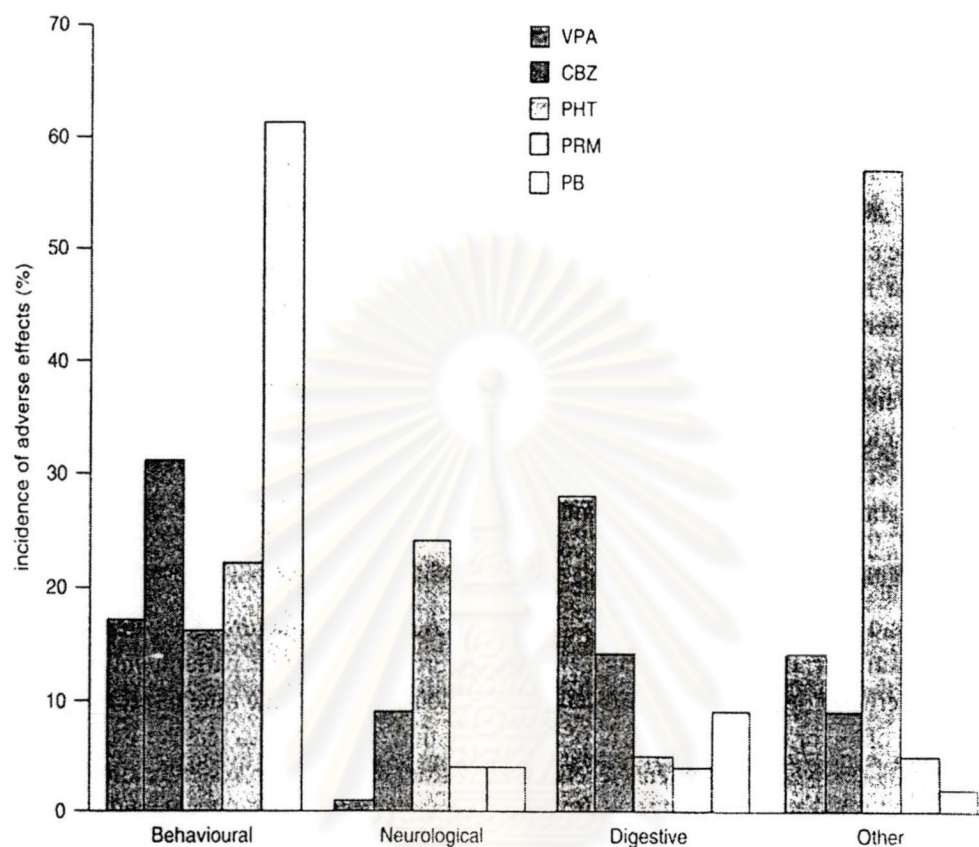
Figure VI Percentage of children with long term (mean 2 years)
single antiepileptic drug with adverse effect

[valproic acid (VPA;n=110), phenobarbital (PB;n=99), primidone (PRM;n=85) phenytoin (PHT; n=63),
or carbamazepine (CBZ;n=35) monotherapy with behavioral, neurological, digestive tract, or other
adverse effects. Other adverse effects: VPA= polyuria, polydipsia, enuresis, alopecia; PB= enuresis,
sweating; PRM= enuresis, sweating, alopecia, hirsutism; PHT= hirsutism(n=22), gingival hyperplasia
(n=21), enuresis; CBZ= polydipsia, polyuria, hisutism]

6.3 Overdose

A number of factors associated with acute drug overdose influence patient outcome, including amount ingested, the time of presentation after ingestion, the ability to remove the drug or prevent it from reaching the systemic circulation, concurent medications and type of medical management. Fatalities due to overdose with valproic acid are rare and recovery has been reported after plasma concentration up to 2120 mg/mL. CNS toxicity, varying from drowsiness to coma, are the most frequently reported effects. At plasma valproic acid concentrations in excess of those achieved therapeutically, symptoms of nausea, vomiting, and dizziness (5-to 6- fold excess) and CNS depression, coma and impaired respiration (10- to 20- fold excess) should be expected. General supportive measures should be applied with particular attention to maintenance of adequate urinary output. Naloxone, in association with intermittent or continuous administration of activated charcoal, has been reported to reverse the CNS depression associated with valproic acid overdosage.

7. Drug Interaction

7.1 Effects of Other Antiepileptic Agent on the Pharmacokinetics of Valproic acid

Steady state plasma valproic acid concentration decrease during coadministration of the drug with hepatic enzyme-inducing agents such as carbamazepine, phenytoin, phenobarbital or primidone. These drugs increase the intrinsic clearance and decrease plasma $t1/2\beta$ values of valproic acid, presumably by enzymatic induction of metabolism. Mean $t1/2\beta$ values of 9 hours or less have been reported in patients with epilepsy receiving enzyme-inducers and valproic acid concurrently, compared with values of 12 to 16 hours for healthy adults taking valproic acid alone. Reduction in plasma valproic acid concentration generally ranged from 30 to 40% in adults and from 40 to 50% in children receiving concomitant hepatic enzyme-inducers antiepileptic drugs. The dosage of valproic acid may need to be increased by 5 to 10 mg/kg/day

when used in combination with other drugs that induce liver enzyme activity. Conversely, when known hepatic enzyme-inducing drugs are discontinued, dosage reduction may be necessary to maintain consistent plasma valproic acid concentrations.

The pharmacokinetic profile of valproic acid is generally not altered by addition of vigabatrin or lamotrigine, although a decline in steady-state plasma valproic acid concentrations was observed during the first 3 weeks of concomitant lamotrigine treatment in 1 trial. When felbamate 1200 or 2400 mg/day was added to the treatment regimen of 10 patients with epilepsy stabilized on valproic acid, the clearance of valproic acid concentrations and area under the concentration-time curve(AUC) values (802 to 1025 and 1236 mg/L.h, respectively) were observed. A downward dosage adjustment of valproic acid may be necessary when felbamate therapy is initiated.

7.2   Effects of valproic acid on the pharmacokineetics of the other antiepileptic agents

Valproic acid is known to inhibit hepatic enzymes and would therefore be expected to increase the plasma concentrations of other antiepileptic drugs. Indeed, a 30 to 40% increase in plasma phenobarbital concentration/phenobarbital dosage ratio has been reported in adults receiving concomitant valproic acid, while a greater increase (52 to 68%) was reported in a paediatric population. An increase in phenobarbital $t1/2\beta$ and inhibition of phenobarbital metabolism by valproic acid has been demonstrated in healthy adult volunteers and in adults with epilepsy. Additionally, the steady-state plasma concentrations of the phenobarbital metabolite derived from primidone increased with the co-administration of valproic acid. Increased sedation, especially in children, is often observed as a result of this interaction; therefore, a phenobarbital or primidone dasage reduction may be warranted.

Two separate and opposing effects of valproic acid on phenytoin disposition have been described.   Valproic acid displaces phenytoin from albumin binding sites which increase the free fraction of phepytoin. Systemic

clearance of phenytoin is enhanced, resulting in reduction in total plasma phenytoin concentration. Hepatic enzyme inhibition by valproic acid decreases phenytoin clearance, which increases both total and unbound plasma phenytoin concentrations. Therefore, in the presence of valproic acid treatment, observed plasma phenytoin concentration within the therapeutic range may actually result in clinical toxicity due to an increase in the unbound phenytoin fraction. Although most patients will not require any alteration in phenytoin dosage, determination of plasma concentrations of unbound phenytoin may become necessary in some patients receiving concomitant valproic acid.

Although valproic acid can inhibit the metabolism of carbamazepine or displace the drug from albumin binding sites, variable effects on plasma carbamazepine concentrations have been reported. Mean increases in plasma concentrations of carbamazepine-10,11-epoxide (CBZ-E), the major active metabolite of cabamazepine, have ranged from 25 to 101% when valproic acid (mean 900 to 1100 mg/day) was given to adults and children receiving carbamazepine monotherapy (mean 1067 to 1820 mg/day).

Valproic acid may increase plasma ethosuximide concentrations by decreasing its metabolism, but this interaction has been observed primarily in patients receiving multiple drug regimens. Interactions between benzodiazepines and valproic acid are not well documented, but a variety of effects have been suggested.

The pharmacokinetic profiles of vigabatrin or gabapentin are generally not altered by valproic acid. Although there are limited published data available, valproic acid appears to reduce the hepatic metabolism of both felbamate and lamotrigine. Dosage requirement of felbamate may be lower in patients receiving hepatic enzyme-inducing antiepileptic drugs.

Other medications

Although there are several small studies and reports of pharmacokinetic interactions with combinations of valproic acid and non-antiepileptic drugs, only few of these findings have demonstrated clinical significance. Valproic

acid may potentiate the CNS depressant effects of alcohol and other CNS depressants. Salicylates have been shown to elevate both total and unbound plasma valproic acid concentration by decreasing valproic acid metabolism and displacing it from plasma albumin binding sites. In vitro, valproic acid displaces warfarin from its plasma albumin binding sites, increasing the active unbound form of drug. Since hematological adverse effects are observed with valproic acid, caution is advised with concomitant administration of anticoagulants or salicylates.

8. Dosage and Administration

Valproic acid, sodium valproate and divalproex sodium are available in capsule,tablet,enteric-coated tablet,sprinkle, liqiud,intravenous and controlled-release formulations for treatment of patients with epilepsy. The recommended initial monotherapy dosage for dosage for adult and children in US is 15 mg/kg/day (maximum 60 mg/kg/day) as necessary until seizures are controlled or adverse effects preclude further increases (Anon. 1993). In the UK and Europe, the adult starting monotherapy dosage is 600 mg daily, increase 200 mg at 3 day intervals until seizure control is achieved (maximum dosage 2500 mg/day). The starting dosage for children weighing>20 kg is 400 mg/day with spaced interval until seizure control is achieved (usually within the range 20-30 mg/kg/day). In children weighing <20 kg , a dosage of 20 mg/kg/day is recommended and in severe cases, may be increased with concurrent plasma valproic acid concentration monitoring. In children requiring dosage above 40 mg/kg/day, clinical chemistry and haematological parameter should be monitored. Enteric coated and controlled-release preparations may be given once or twice daily, while uncoated and liquid preparations of valproic acid have commonly been administrated in 3 or 4 divided doses to minimise fluctuations in plasma concentrations, particularly in patients receiving polytherapy with hepatic enzyme-inducing antiepileptic drugs. Gastrointestinal irritation may minimised by administration with or after food or by slowly increasing the dosage from an initial low level. Tablets or capsules should be

swallowed whole to avoid local irritation of the mouth and throat. The intravenous formulation has been used in patients with epilepsy for whom oral therapy is temporarily not possible, such as neurosurgical patients (Moore et al. 1989), in neonates with convulsions. The oral solution has also been administratered rectally when oral administration is unsuitable or in the treatment of refractory status epilepticus. Therapeutic plasma valproic acid concentration for most patients will range from 40 to 100 mg/L.

Due to the possibility of interactions with other antiepileptic medications, the dosage of valproic acid and that existing medications must be closely monitored during treatment. In order to drug interactions, the dosage of carbamazepine, phenobarbital, phenytoin and felbamate may require reduction when valproic acid is added to the treatment regimen, based on clinical observations and steady-state plasma drug concentrations. Initial and maintenance dosages of lamotrigine should be reduced by 50% upon addition to existing valproic acid therapy.

Valproic acid is contraindicated in patients with hepatic disease to significant hepatic dysfunction (Anon, 1993). The patients at highest risk for developing fatal hepatotoxicity include children aged ≤ 2 years, patients receiving multiple antiepileptic drugs, patients with genetic metabolic disorders (carnitine or ornitine carbamoyltransferase deficiency and/or familial history of severe hepatic disease), and patients with severe epilesies involving cerebral lesion, mental retardation or other associated hereditary pathology. These incidents usually occurred during the first 6 months of therapy and usually involved polytherapy. In these patients, valproic acid should be used with extreme caution and as a sole agent.

Dosage requirements may be slightly decreased in the elderly while dosage adjustments based on total plasma drug concentrations should be made cautiously in the elderly and in patients with renal impairment or uncompensated diabetes mellitus.

An increased risk of neural tube defects has been demonstrated in offspring born to mothers receiving valproic acid during the first trimester. The

benefits of antiepiliptic therapy during pregnancy must be evaluated against the possible risks and patients should be informed of these and the need for screening. Intensive prenatal monitoring (α-fetoprotein determination, amniocentesis and ultrasonography), dividing the dosage or using controlled-release formulation, folic acid supplementation and, if possible, dosage reduction, should be considered when the use of valproic acid during pregnancy cannot be avoided

Patients receiving valproic acid should be monitored for platelet count and coagulation parameters before initiating therapy, at periodic intervals and prior to planed surgery.

9. Place of valproic acid in therapy

Epilepsy is serious, chronic neurological disorder which is estimated to occur in about 1% of the general population. Treatment of epilepsy relies upon pharmacological intervention after careful assessment and classification of seizure type. With the ultimate goal being to preserve the patient's quality of life, the success of antiepileptic drug therapy depends on educating patients about their disorder and controlling seizure (preferably with monotherapy), with minimal adverse effects.

The efficacy of valproic acid in the treatment of generalized seizure (absence, myoclonic and tonic-clonic) was demonstrated in early non-comparative clinical trials of polytherapy and monotherapy, while partial seizures showed less response. However, subsequent comparative clinical trials supported the use of partial seizures. Valproic acid has demonstrated similar efficacy to ethosuximide in the treatment of absence seizures, and carbamazepine, phenytoin and phenobarbital in the treatment of both tonic-clonic and partial seizures. Oral valproate has been proven efficacy in preventing episodic and chronic migraine, controlling seizures, and modulating mood swings in bipolar illness.