New Approach in the Treatment of Epilepsy : Efficacy of New Antiepileptic Drugs

Dae Hie Lee, M.D.*†

ABSTRACT

To consider current concepts of epilepsy further, the brief review begins with a discussion of what is epilepsy, discribes multifactorial nature of epileptic disorders, and ends with a presentation of current classifications. A combination of the standard antiepielptic drugs(AEDs) may be necessary to treat intractable seizures, but no studies have been done to indicate an optimal combination. The new AEDs provide alternative choices, but questions remain about the optimal timing and manner of administration. AEDs selection must individualized, no drug of choice can be named for all patients.

KEY WORDS : Current concepts of epilepsy · New AEDs.

Introduction

Epilepsy is best viewed, not as a single condition, but rather as a symptom of neurological disorder. The clinical manifestations depend upon the cause of the epilepsy, the anatomical location within the brain of the epileptic focus, the pattern of spread of epileptic discharges through the brain, and also on the age and the level of cerebral maturity of the patient. Epilepsy is characterized by recurrent seizures, as a chronic illness. Many epilepsies with focal seizures as well as convulsive generalized seizures respond satisfactorily to antiepileptic drugs(AEDs) that reduce repetitive firing or that augment GABAa-mediated inhibition. However, the proba-bility of relapse were mostly around 40% by several years after discontinuation of antiepileptic drugs. The other hand, epilepsies with a recurrent seizure despite AEDs continuation after a certain remission period might have a different nature from those with a relapse seizure. The true intractable epilepsies may be established about 5 - 10% of patients on optimal AEDs treatment. A cumulative incidence of about 135 per 100,000 population has been calculated for epilepsies that disable the patient despite relevant AEDs treatment.

With the recent or anticipated introduction of new antiepileptic drugs, a wide array of medications is available to prevent the recurrence or decrease the severity of convulsive or nonconvulsive seizures. Converging evidence from many studies has made increasingly clear the advantages and disadvantages of the well-established AEDs, including carbamazepine, ethosuximide, phenytoin, primidone and valproate. Most of the new AEDs are different from the older ones in their mechanisms of action, pharmacokinetics, and adverse effects, which may mean that they eventually will find an important place in the treatment of epilepsy.

Efficacy as a Selection Factor

The selection of an AED is based primarily on its efficacy for specific types of seizures and epilepsy. Certain epileptic syndromes can be recognized on the basis of a constellation of characteristics, including not only types of seizures but also age, EEG findings, and etiology. Classification of seizure type and epileptic syndromes have been proposed by the International League Against Epilepdy(ILAE). Although the efficacy and the frequency or severity of adverse effects are primary considerations in the selection of an AED, other factors may be espec-

*본 연구는 1997년도 인제연구비 지원에 의해 이루어졌음.
**Department of Neurology, Anam Hospital, College of Medicine, Korea University, Seoul, Korea*
†*Corresponding author :*
126-1 AnamDong 5ka, Sung Buk-Ku Seoul, 136-705, Korea
Tel) (02) 920-5353, Fax) (02) 923-5908

ially important for some indiviuals or populations. It is expected that the standard AEDs will be used until they fail to provide good treatment or until cumulative evidence from controlled clinical trials suggests that one of the newer compounds should be the AED of first choice. So, these classifications provide our best current understanding and serve as a frame of reference for communication.

Classifications

The method of classification which is now most widely used is a discriptive scheme based on the clinical and EEG manifestations of the seizures, devised by the ILAE. This was first proposed in 1970 using 6 criteria for classification : clinical form, interictal EEG, ictal EEG, anatomical substrate, age, and etiology. In 1981, a revison was proposed, and officially adopted in 1982. In recognition of the limitations of a seizure type classification, the ILAE proposed a new compound scheme.

As with the classification of the seizure type, the epilepsies are divided into two major grouping according to whether or not there is a generalized or focal origin to the seizures. A third category of epilepsies which are undertermined whether generalized or focal is also included, and there is a fourth category of special syndromes(Table 1).

Table 1. The ILAE classification of the epilepsies and epilepsy syndromes

Ⅰ. Localization-related(focal, local, partial) epilepsies and epileptic syndromes
A. Idiopathic with age-related onset
1. Benign childhood epilepsy with centrotemporal spikes
2. Childhood epilepsy with occipital paroxysms
B. Symptomatic
Ⅱ. Generalized epilepsies and epileptic syndromes
A. Idiopathic with age-related onset
1. Benign neonatal epilepsy
2. Juvenile myoclonic epilepsy(impulsive petit mal)
3. Juvenile absence epilepsy with generalized tonic-clonic seizures on awakening
B. Secondary(idiopathic or symptomatic)
1. West syndrome(infantile spasms)
2. Lennox-Gastaut syndrome
C. Symptomatic
1. Nonspecific etiology(early myoclonic encephalopathy)
2. Specific syndromes(epileptic seizures that may complicate many diseases, e.g., Ramsay-Hunt syndrome, Unverricht's disease)

Modified and abbreviated from Commission(1989)

1. Localization-related epielpsies and epileptic syndromes

= Partial seizures =

(Features of partial epilepsy arising in different anatomical regions)

1) Partial seizures arising in the temporal lobe

The commonest pathology underlying this type of epilepsy is hippocapal sclerosis. This pathology is associated with febrile convulsions in young children, possibly predisposing the child to febrile seizures or as the result of a complex febrile convulsion.

2) Epilepsy arising in the frontal lobe

Seizures of frontal lobe origin can take the form of complex partial seizures, simple partial seizures, and secondary generalized attacks.

3) Epilepsy arising in the central region

These seizures can occur in clear consciousness(simple partial seizures) or with impairment or loss of consciousness(complex partial seizures).

4) Epilepsy arising in the parietal and occipital lobes

Focal seizures arise from foci in these locations less commonly than from frontal and temporal regions.

2. Childhood epilepsy syndromes

Localization-related epilepsy, idiopathic

Epilepsies and syndromes undetermined as to whether focal or generalized

Special syndromes

Generalized idiopathic epilepsies

1) Neonatal seizures

The clinical and EEG features, the cause and the auatomicopathologicar basis of neonatal epilepsy different from those of the epilepsies of later childhood or adult life.

2) Infantile spasm(West's syndrome)

The spasms rarely develop before the age of 3 months, 90% start in the first year of life, and the peak incidence is at 4 - 6 months. Neurological deficit is present before the onset of spasms in up to 80% of patients. The spasms are usually generalized, but can be asymmetrical or even unilateral. In about 2/3 of patients the interictal EEG exhibits hypsarrhythmia.

3) Febrile convulsions

4) Childhood myoclonic epilepsy syndromes

In most cases, no cause for the epilepsy is identifiable. Sym-

ptomatic myoclonic epilepsy may be caused by various presental pathologies and less often perinatal injury.

5) Benign rolandic epilepsy and other benign epilepsy syndromes

Benign rolandic epilepsy is a well difined childhood syndrome accounting for up to 15% of all childhood epilepsies. The age of onset is between 3 and 13 years. The seizures are typically facal, involving the face and oropharynx, often with secondary generalization, and have a strong tendency to occur during sleep.

6) Eletrical status epilepticus during slow wave sleep(ESES)

This syndrome is defined by the presence on EEG of generalized spike/wave discharges occupying at least 85% of non-REM sleep.

7) Acquired epileptic aphasia(Landau-Kleffner syndrome)

The aphasia may evolve in a subacute or gradual fashion, over weeks or years. In 70% of cases, this develops before the age of 6 years.

8) Lennox-Gastaut syndrome

The clinical and EEG picture can occur in mild and severe forms, can evolve from other types of epilepsy and can be caused by a great number of different pathological disorders. The disorder is characterized by severe epilepsy and mental deterioration. And seizures are frequent and severe, atypical absence, tonic, myoclonic and tonic-clonic in form or in combination. The age of onset is generally between 1 and 7 years. The EEG shows 1 - 2.5Hz spike and wave complexes with other abnormalities and abnormal background rhythms, without photosensitivity. The syndrome has a multitude of causes and the prognosis is dependent upon the etiology, but in general outcome is poor.

3. The idiopathic generalized epilepsies

The idiopathic generalized epilepies(IGEs) are a spectrum of epileptic conditions with a genetic basis and characteristic clinical symptoms. It has been estimated that IGEs comprise 10% of all epilepsies and 40% of those with tonic-clonic seizures.

The genetic contribution both to the clinical and eletrographic features of IGE has been intensively studied.

1) Childhood absence epilepsy(CAE)

Absence may be noted hundreds of times a day(pyknolepsy), last a few seconds, usually less than 15, and comprise a blank stare and unresponsiveness.

2) Juvenile absence epilepsy(JAE)

JAE is approximately 1/4 as common as CAE and the age of onset has been arbitrarily set at 10 years. Absence tend to be less frequent than in CAE, but of longer duration and associated with a less profound impairment of consciousness. Up to 80% of patients with JAE develop generalized tonic-clonic seizures (GTC).

3) Juvenile myoclonic epilepsy(JME)

JME comprises 5 - 10% of cases of epilepsy. A common presentation is of a teenager who has his first generalized tonic-clonic seizure on awaking, after little sleep, following a late night party or consuming a large amount of alcohol. The types of seizures occur myoclonic, GTC, and absence. The EEG shows 4 - 6Hz polyspike and slow-wave generalized discharges that last up to 20 s with normal background activity. Up to 90% of patients with JME become seizure free with optimal medication, but a very high relapse rate if medication is withdrawn. There are a evidence for the existence of a locus predisposing individuals to JME on chromosome 6p, and the locus has been designated EJM1.

4) Epilepsy with generalized tonic clonic seizures on awakening(GTCA)

They have reported 16 - 50% of GTC. The age of onset is usually between 9 and 25 years, with a peak at the time of puberty. About 50% of patients have absence and 30% have myoclonic seizures. The usual definition of seizures on awakening is taoken as " within 2 h of waking from sleep ", whatever time of day this occurs.

5) Eyelid myoclonia with typical abences(EMA)

Eyelid myoclonia with typical absence(EMA) is an IGE syndrome that is not yet recognized by the ILAE. EMA is similar to CAE.

4. Progressive myoclonic epilepsy

1) Lafora body disease

The age of onset of Lafora body disease is between 6 and 19 years. Progressive myoclonus is associated with tonic-clonic and partial seizures and severe dementia, often with focal cognitive features. The histopathological marker is the presence of Lafora bodies. More recently, linkage analysis performed in 9 families with Lafora's disease produced a maximum two-point lod score

of 10.54 at θ =0 at the marker D6S311, localizing the gene to 6q23 - 25.

2) Unverricht-Lundborg disease

Th onset is between the ages of 6 and 15 and it is an autosomal recessive condition. Linkage studies have placed the gene on chromosome 21. It presents as myoclonus, initially easy to control but then progressively worsening. Tonic-clonic seizures are infrequent, but ataxia and tremor deveop and may become predominant.

3) Mitochondrial disease

Maternally inherited defeats in mitochordrial metabolism can produce myoclonic epilepsy and ragged red fibers(ME RRF) syndrome

4) Neuronal ceroid lipofuscinosis

Neuronal ceroid lipofuscinosis is an euzyme deficiency, qeuerally inherited autosomal recessively, in which lysosomal inclusions are found in lympho cytes, skin, muscle, liver and brain.

5) Dentatorubropallidoluysian atrophy(DRPLA)

Thid autosomal domiuant condution is a comparatively common form of PME. Deueutia and corebellar atatia are prourinant and other pypamidal and extra pyramidal motor sigus and psychiatric disfurqance also develop.

6) Others

5. The genetic epilepsies

The statement of " a family history of seizures " frequently does not specify if the type of seizure is the same as in the proband or another seizure type. The term " idiopathic " is defined as " no known or suspected etiology, other than possible hereditary predisposition ", whereas " symptomatic " indicates that a disorder is known or suspected. Originally, epilepsies and epileptic syndromes, in which genetics were believed to play a role, were classified as generalized and idiopathic.

Mechanisms of Action of Currently Available Antiepileptic Drugs

1. The known major mechanisms of actions of the drugs

1) Use-dependent block of sodium channels
2) Ehancement of GABA-mediated inhibition
3) Inhibition of a subclass of voltage-dependent Ca channels(T channels)

1) Use-dependent inhibition of voltage-dependent sodium currents

Phenytoin(PTH), carbamazepine(CBZ), phenobarbital(PB), and sodium valproate(VPA) all have the ability to inhibit the voltage-dependent Na current which is responsible for the action potential in nerve cells in the brain. This inhibition occurs at drug concentrations which are close to those seen in the therapeutic range in vivo.

In order for these drugs to work, the channel must first be opened(the block is use dependent). Thus, these drugs have little or no effect on single action potentials, but when a neuron begins to fire repetitively, the later action potentials of a group become smaller and finally are blocked. The reduction in repetitive firing also produces a decrease in various forms of potentiation at synaptic ending which may also contribute to the antiepileptic effect of these drugs.

2) Enhancement of GABAa receptor-mediated inhbition

The second well established mechanism of action for AEDs is an enhancement of GABAa receptor-mediated inhibition. Both PB and benzodiazepines(BDZ) can do this, although with different molecular mechanisms. GABAa-mediated inhibition is the most powerful and important form of inhibition in the mammalian forebrain. All agents which reduce this form of inhibition produce seizures in animals and all agents which can be shown to enhance GABA-mediated inhibition are antiepileptic at some level. GABA acts at a GABAa receptor to open chloride channels and produce neuronal hyperpolarization. The GABAa receptor is known to certain several allosteric modulatory site and can be up or down regulated by commonly used drugs. The BDZs act to enhance inhibition by increasing the frequency with which GABA-activated chloride channels open, and thereby produce larger inhibitory events, although not necessarily longer ones. The BDZs do not seem to have the ability to produce other cellular events which may be antiepileptic effects.

3) Block of voltage-dependent Calcium current

The third known mechanism of action of AEDs is inhibition of one form of voltage dependent calcium currents(T-currents). T-currents are activated when a neuron is mildly deporized and are transient. They are often inactivated near the normal resting membrane potential. Therefore, a neuron must first be hyperpolarized to remove the inactivation before the current can be

activated by a subsequent depolarization. Thus, this current appears to be designed to play the role of a rhythmic pacemaker in neurons which undergo cycles of depolarization and hyperpolarization. In some neurons in deep thalamic and diencephalic structures, these currents can be very large and can contribute to spontaneous burst firing activity. The ability of ethosuximide (ESM) to selectively block these currents at therapeutically appropriate concentrations suggests that this is the mechanism of action by which this class of drugs acts. Despite VPA's ability to suppress the same kinds of seizures, it does not appear to have any effect on these currents.

2. New strategies for AED development

1) Mechanism specific AED development
2) Drugs which affect the GABA inhibitory system
3) Drugs which affect excitatory systems
4) Drugs which affect other neuromodulatory systems

1) Mechanism specific AED development

In the 1980's and 1990's, antiepileptic drug development has taken a new turn. There has been a recent explosion of information about basic neuroscience and basic mechanisms of epilepsy. This new research has led to a number of hypothesis relating to the development of the increased excitability which is the underlying cause of epilepsy, and into the mechanisms by which seizures develop in areas of local hyperexcitability and then spread to nearby and distant areas of normal brain.

When GABA's effects in the brain are reduced for any reason, seizures develop. This can occur if neurons synthesize less GABA, if the neurons which utilize GABA are injured or die in response to trauma, infection or hypoxia or if GABAa receptors are blocked. Conversely, enhancement of GABA-mediated inhibition is antiepileptic.

The other major group of neurotransmitters in mammalian CNS involved in information transfer, and under pathophysiological conditions, in the development of epilepsy, are the excitatory amino acids. Glutamate and aspartate are thought to be the major excitatory neurotransmitters in the mammalian CNS. These sustances act on several types of neurotransmitter receptors present on both postsynaptic neurons and presynaptic nerve terminals. There are at least 3 major classes of excitatory receptors coupled to ion channels, which when activated increase excitability in the receptorbearing cell. These receptors have been named after the compounds which selectively activate them: AMPA, NMDA, and kainate. In addition, there are "metabotropic" glutamate receptors on neurons, which when activated affect second messenger systems and thereby indirectly affect excitability.

2) Drugs which affect the GABA inhibitory system

The system which has proven to be most amenable to direct attack is the GABA inhibitory system. Compounds have been developed which act as suicide enzyme inhibitors of the main GABA metabolizing enzyme, GABA transaminase. These agents are relatively inactive in their native form but can bind to the transaminase enzyme and become activated to become compounds which will form convalent bonds with the enzyme and irreversibly inactive it. These drugs therefore are relatively specific for GABA utilizing systems and can enhance inhibition in the CNS. Gammavinyl GABA(GVG) or Vigabatrin (VGB) is the first drug of this class to be involved in clinical trials. GVG will increase GABA levels in the brain and this GABA is then able to interact with both the GABAa and GABAb systems(Fig. 1).

A second stratergy for enhancing GABA's inhibitory effects in the brain, is to prevent the reuptake of GABA which is released at synaptic terminals. A group of GABA uptake inhibitors has been synthesized and these agents have been shown to be effective in a variety of animal seizure models. One such agents, Tiagabine, is now entering clinical trials. This drug will also not be "receptor specific" and will act to increase GABA availability at all sites of release and in proximity to all receptor subtypes. However, the exact mode of action of gabapentin (GBP) is unknown, although studies suggest that it may promote GABA synthesis.

A third strategy which has been employed to enhance GABA mediated inhibition is to deliver GABA directly to receptors in the CNS. GABA itself will not pass the blood brain barrier very effectively so a number of compounds have been developed which can act like GABA, yet cross the blood enter the CNS, and then be metabolized to GABA. Progabide is such a drug

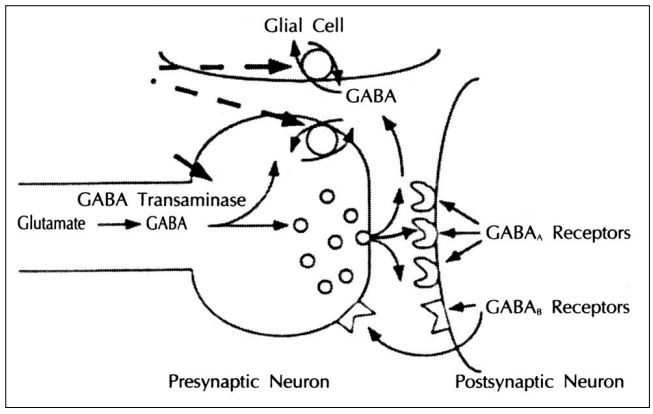

Fig. 1. The postsynaptic neuron and GABA receptors.

and appears to directly activate the GABAa receptor(Fig. 2).

3) Drugs which affect excitatory systems

Agents which work at excitatory amino acid receptors are being very actively developed by a number of pharmaceutical companies and neuroscience laboratories. The first target for these drugs was the NMDA receptors, as it was the best characterized receptor, a variety of regulatory sites exist on it, and it has been implicted in both epilepsy and excitotoxic neuronal damage. The NMDA receptor component of excitatory transmission appears to play a role in slowly developing proccesses rather then in rapid information transfer within the CNS. The NMDA receptor has a number of binding sites which can serve as pharmacological modulatory influences. In addition, activity of the receptor is affected by pH and oxidation-reduction and the presence of polyamines, which are natural brain costituents.

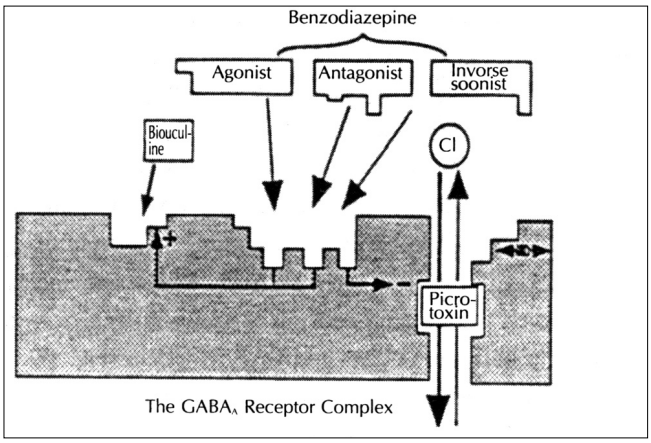

Fig. 2. The GABAa receptor complex.

All agents which block NMDA receptor function in vitro have proven to be antiepileptic in animal models of seizures. For example, MK-801 is an open channel blocking agent, related to ketamine. It is a very effective antagonist of NMDA mediated responses and had a brief clinical trial as and antiepileptic drug (Fig. 3).

4) Drugs which affect other neuromodulatory systems

The agents which act at the adenosine receptor or on the adenosine synaptic system(e.g. blocking adenosine uptake) have been shown to be effective antiepileptics in animal models.

Efficacy of Established and New Antiepieltic Drugs

1. Generalized epilepsies and epileptic syndromes

1) Idiopathic epilepsies

VPA is usually the drug of choice for the generalized idiopathic epilepsies. Its efficacy is equal or greater than that of CBZ or PHT for tonic-clonic seizures and equal to that of ESM for absence seizures. VPA is the only AED that can control seizure types when patients have combinations of tonic-clonic, absence, and /or myoclonic seizures.

(1) Absence seizures

Absence seizures respond well to both ESM and VPA. Controlled clinical trials indicate that either AEDs can effect marked or virtually complete seizure control in 70% to 90% of

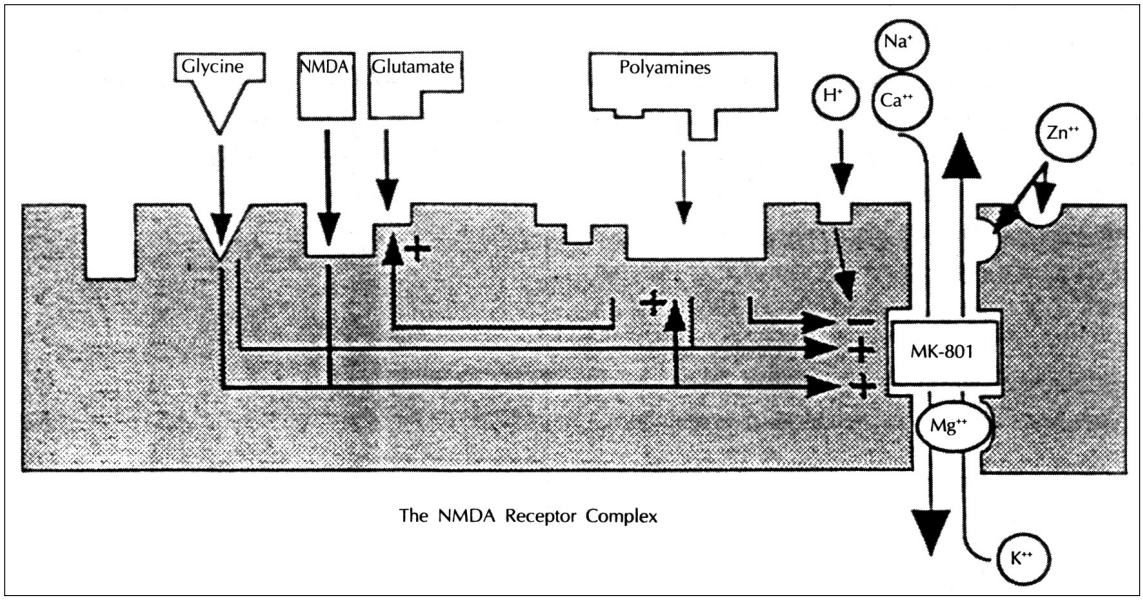

Fig. 3. The NMDA receptor complex.

patients. Although efficacy is comparable between the two AEDs, ESM is usually selected for patients with pure childhood absence epilepsy. For more difficult problems, a combination of the two AEDs may provide better control. Acetazolamid(AZM) is moderately efficacious, although no controlled trials are available. Similarly, the BZDs, including diazepam(DZP), clonazepam(CZP), and nitrazepam(NZP), provide good control but may lose efficacy after several months of administration.

(2) Myoclonic seizures

Despite the variable probability of good control with treatment, VPA is the AED of choice in most cases. The BZDs are quite effective but cause sedative side effects, and in many patients some loss of efficacy is noted after several months.

(3) Primary generalized tonic-clonic seizures

Seizures in 75 - 85% of patients can be completely controlled with VPA monotherapy. Control was the same or better than that obtained with administration of PHT or CBZ. In refractory patients with generalized idiopathic epilepsy, Mattson (1995) was able to obtain complete seizure control with VPA monotherapy in 80% of patients who had not responded to CBZ, PB, PHT, or a combination of these AEDs, in addition to ESM or BZDs. This high success rate was achieved only after a lengthy crossover and high dosages of VPA initially.

2) Secondary symptomatic epilepsies

(1) West syndrome

Adrenocorticosteroid hormone(ACTH) or corticosteroids are usually considered the treatment of choice. Controversy continues as to whether ACTH or corticostroids have a better effect on the long-term outcome than AEDs such as VPA. Some early evidence suggests that VGB may be helpful in this syndrome.

(2) Lennox-Gastaut syndrome

In this syndrome, treatment is difficult with any sigle AED or combination of AEDs. VPA has the greatest spectrum of activity for treatment of the multiple seizure types. The dosage should be increated until side effects appear. CBZ, PHT, and PB may be useful in controlling the tonic-clonic or tonic seizures, CZP or other BZDs are quite effective, at least temporarily, in controlling the myoclonic or absence attacks, and ESM is effective for treatment of the absence. In controlled clinical trials, felbamate(FBM) has proven to be effective in this syndrome and results in major improvement. One study also suggests that lamotrigine(LTG) may be especially helpful in Lennox-Gastaut syndrome.

2. Localization-related epilepsies and epielptic syndromes

It is reasonable to select the AEDs most lkely to provide optimal efficacy against both types of seizures. In general, CBZ and PHT show the best balance of seizure control, with fewer adverse effects than PB or PRM, for the treatment of partial seizures. However, a study found better efficacy and better overall long-term outcome for CBZ than VPA.

1) Idiopathic benign childhood epilepsy with centrotemporal spikes

When treatment is advisable, CBZ or PHT is quite effec-tive, and complete control is often possible with a modest dosage. No controlled, comparative clinical trials of VPA have been performed in this group.

2) Symptomatic epilepsies

(1) Secondary generalized tonic-clonic seizures

In the study of patients with partial epilepsy and secondary generalized tonic-clonic seizures, equal efficacy for CBZ, PB, PHT, and PRM was found with follow up for 3 years. Comparative study of the efficacy of VPA indicate that VPA also is comparable to the other AEDs in preventing secondarily generalized tonic-clonic seizures.

(2) Partial seizures

CBZ, PB, PRM, and PHT showed few differences in efficacy for treatment of partial seizures. However, there was no statistically significant difference between CBZ and PHT or PHT

Table 2. Commonly used starting and maintenance doses of AEDs

AED	Starting dose(mg)	Average maintenance dose (Total mg/day)	Doses/day
Acetazolamide	250	500 - 1000	2
Carbamazepine	100	600 - 1800	2 - 4 (Retard : 2)
Clobazam	10	10 - 30	1 - 2
Clonazepam	0.5	0.5 - 3	1 - 2
Ethosuximide	250	500 - 1500	1 - 2
Felbamate	1200	2400 - 3600	2
Gabapentin	300	900 - 2400	3
Lamotrigine	50	200 - 400	2
Oxcarbazepine	300	900 - 2400	2 - 3
Phenobarbitone	60	60 - 180	1
Phenytoin	200 - 300	200 - 400	1 - 2
Piracetam	7200	12,000 - 2400	3
Valproate	500	1000 - 2500	1 - 2
Vigabatin	500	2000 - 3000	1 - 2

Table 3. Selection of new antiepileptic drugs

Drug	Advantages	Disadvantages	Comment
Gabapentin	Effective in partial and tonic-clonic seizures ; well tolerated	Limited absorption ; short half-life ; moderate efficacy	Mechanism of action unknown, but perhaps enhanced GABA synthesis or release
Felbamate	Broad spectrum of efficacy ; effective in Lennox-Gastaut syndrome ; alerting	Rare fatal aplastic anemia and hepatitis ; headache ; insomnia ; vomiting and weight loss	Choice limited due to risks ; interacts with and inhibits metabolism of other antiepileptic drugs
Lamotrigine	Broad spectrum of efficacy ; sense of well-being	Hypersensitivity reactions ; metabolism inducible	Extensive experience
Oxcarbazepine	Very effective in partial and tonic-clonic seizures	Sensitivity reactions ; hyponatremia	Fewer interactions than carbamazepine
Tiagabine	Effective in partial and tonic-clonic Seizures	Hepatic metabolism ; short half-life	Unique mechanism of action : blocks GABA reuptake
Vigabatrin	Effective in partial and tonic-clonic seizures ; infantile spasms	Uncommon but apparently important psychiatric symptoms	Unique mechanism of action : irreversibly inhibits GABA transaminase

and PB. The other hand, CBZ had greater efficacy in complex partial sdeizures, as measured by seizure no., seizure rate, rating score, and time to first seizure. Other studies have found no differences in the efficacy of CBZ and VPA for treatment of complex partial seizures(Table 2).

3. Special epileptic syndromes

1) Alcoholic epilepsy

When parenteral administration is necessary, intravenous DZP or LZP is preferable. PB also shows cross tolerance to alcohol and is effective. Both PHT and CBZ have been administered with inconsistent results, PHT is usually not effective.

2) Febrile convulsion

The efficacy of PB in long-term treatment has been demonstrated, the intermittent use of DZP orally or rectally reduces the frequency and severity of recurrent seizures.

4. NEW AEDs

Felbamate and topiramat have broad-spectrum antiepileptic activity and can be considered for treatment of partial seizures and tonic-clonic seizures. On the other hand, gabapentin has a fairly specific spectrum of antiepileptic activity. Lamotrigine and tiagabine are effective for controlling partial and generalized siezures.

The adantages and disadvantages of the new AEDs are incompletely defined. FBM, GBP, LTG, oxcarbamazepine(OCBZ), and VGB have all shown efficacy in treatment of intractable epilepsy when administered as adjuncts to one or more standard AEDs. The new AEDs provide alternative choices, but questions remain about the optimal timing and manner of administration. Comparing the efficacy of these AEDs is difficult, and some design differnces in clinical trials complicate estimates of their relative efficacy. Nevertheless, as a group, the new AEDs appeared to produce a 50% reduction in seizures in about 30% of patients in short term, controlled, add-on trials, with outcomes significantly better than placebo(Table 3).

Summary

Antiepileptic drug selection is based primarily on efficacy for specific seizure types and epileptic syndromes. For idiopathic generalized epilepsies with absence, tonic-clonic, and myoclonic seizures, the AED of choice is valproate. Secondarily generalized epielpsies with tonic, atonic, and other seizure types are difficult to treat with any single AED or combination AEDs. The AEDs of choice for absences are ethosuximide and valproate. For control of primary GTC seizures, any of the other major AEDs can be effective. If VPA cannot be prescribed, carbamazepine, phenobarbital, phenytoin, or primidone may be effective, but ethosuximide or a benzodiazepine must be added to control associated absence or myoclonic seizures. The AEDs of first choice for partial epilesies with partial and secondarily GTC seizures are carbamazepine and phenytoin. Increasing evidence suggests that valproate is a good alternative when carbamazepine and phenytoin fail. A combination of two of the five standard AEDs may be necessary to treat intractable seizures, but no studies have been done to indicate an optimal combination. Other epilepsy syndromes such as neonatal and infantile epilepsies, febrile epilepsy, alcoholic epilepsy, and status epilepticus require specific AEDs treatment. AED selection must individualized. No " drug of choice " can be named for all patients.

참고문헌

Dreifuss FE(1994) : *New antiepileptic drug development. Epilepsia*

35 (suppl. 5) : S6-S9

Duncan JS, Shorvon SD, Fish DR (1995) : *Clinical epilepsy. New York. Churchill Livingstone*

Gustavson L, Mengel H (1995) : *Pharmacokinetics of Tiagabine, a gamma-aminobutyric acid uptake inhibitor, in healthy subjects after single and multiple doses. Epilepsia 36 (6) : 605-611*

Harden C, Trifiletti R, Kutt H (1996) : *Felbamate levels in patients with epilepsy. Epilepsia 37 (3) : 280-283*

Hosford DA, Caddick SJ, Lin F (1997) : *Generalized epilepsies : emerging insights into celluar and genetic mechanisms. Curr Opin Neurol 10 (2) : 115-120*

Leppik IE, Graves N, Devinsky O (1993) : *New antiepileptic medications. In : Devinsky O (ed). Epilepsy I : Diagnosis and treatment, Neurologic clinic vol 11. no 4. Philadephia. W.B. Saunders 923-950*

Macdonald RL, Greenfield LJ (1997) : *Mechanisms action of new antiepileptic drugs. Curr Opin Neurol 10 (2) : 121-128*

Marson AG, Chadwick D (1996) : *Comparing antiepileptic drugs. Curr Opin Neurol 9 (2) : 103-106*

Matsuo F, Gay P, Madsen J, Tolman KG, Rollins DE, Risner ME, Lai AA (1996) : *Lamotrigine high dose tolerability and safety in patients with epilepsy : a double blind, placebo controlled, eleven week study. Epilepsia 37 (9) : 857-862*

Mattson RH (1995) : *Efficacy and Adverse effects of estableshed andnew antiepileptic drugs. Epilepsia 36 (suppl. 2) : S13-S26*

Mattson RH (1998) : *Medical management of epilepsy in adults. Neurology 51 (suppl. 4) : S15-S20*

Sander JW (1998) : *New drugs for epilepsy. Curr Opin Neurol 11 (2) : 141-148*

Waterhouse E, Delorenzo RJ (1996) : *Mechanisms of action of antiepileptic drugs : an overview. In : Shorvon S, Dreifuss F, Fish D, Thomas D. eds. The treatment of epilepsy. Oxford Blackwell Science 123-137*