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New Antiepileptic Drugs
—I. Basic Characteristics—

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Epilepsy management starts with drug therapy. Since C.Locock first demonstrated the clinical efficacy of bromide on epilepsy in 1857, numerous antiepileptic drugs(AEDs) had been developed, however, a majority of them were withdrawn either due to unacceptable toxicities or unsatisfactory efficacies. Therefore, the AEDs in current use(conventional AEDs) are, in fact, true survivors passed through the tough postmarketing surveilences conducted over past several decades.

Among conventional AEDs, phenytoin(PHT), carbamazepine(CBZ), valproic acid(VPA), and phenobarbital(PB) are the major AEDs comprising more than 90 % of prescriptions. Ethosuccimide(ESM) is still the primary drug for absence seizure. Benzodiazepines(BDZ : clonazepam and clobazam) are widely used for various types of medically resistant epilepsy but they are best regarded as secondary AEDs for their sedating side effects and development of tolerance in long-term use.

The drug management of epilepsy has been fully refined and optimized lately due to the major advances of clinical epileptology which includes : 1) development of classification systems of epileptic seizures and syndromes, 2) widely available measurement of blood levels of AEDs with improved acknowledgement of pharmacokinetics, and 3) introduction of monotherapy and recently rational polytherapy. With these development, about 80 % of newly diagnosed epilepsy can achieve prolonged sizure remission by appropriate AED therapy, which has changed the concept of epilepsy from "chronic illness" to "treatable illness" (*Annegers et al., 1979 ; Elwes et al., 1984*).

Despite these development, conventional AEDs have still significant shortages as follows ; 1) the efficacy of conventional AEDs is still less than satisfactory for partial seizures. The remission rate is about 65 % by the best monotherapy (*Mattson, 1994*). The efficacy of major AEDs in partial seizures is quite comparable each other and the choice of drug is determined primarily by the degree of side effects (*Turnbull et al., 1982 ; Mattson et al., 1985 ; Richens et al., 1994*). 2) the efficacy of conventional AEDs is quite limited in severe epileptic syndromes such as West syndrome, Lennox-Gastaut syndrome, IMSD's, myoclonic epilepsies etc. 3) the incidence of side effects of conventional AEDs is higher than 50 % and 5 % is potentially serious life threatening systemic side effects (*Collaborative Group for Epidemiology of Epilepsy, 1986 ; Bourgeois, 1994*). All AEDs have dose-related cognitive side effects with sedating AEDs (PB, Primidone, BDZs) having the most (*Smith, 1991*). 4) conventional AEDs pocesses significant potentials for drug interactions which are problematic for polytherapy, 5) conventional AEDs were not proven to have prophylactic effects on epileptogenesis (*Temkin et al., 1990*) and the data from epidemiological studies in underdeveloped countries (*Feksi et al.,1991 ; Placencia et al., 1992*) as well as AED withdrawl studies (*MRC antiepileptic withdrawl study group, 1991*) do not suggest any influence on the natural course of epilepsy, thus they belong to the category of "symptomatic therapy".

Considering these shortages of conventional AEDs with the estimation of at least 5 million patients being suffering from epileptic seizures refractory to conven-

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tional AEDs worldwide, it seems quite obvous that we certainly need better AEDs. Since VPA was approved in UK in 1976, no new AEDs had been introduced to the market until 1989. The time interval was the pregnant period of new AED era. With the accumulation of knowledge about the pathomechanisms of epilepsy, new compounds were developed and screened at the laboratory to be subjected for the process of rational clinical trials. In 1989, vigabatrin and zonisamide were introduced in UK and Japan respectively, which was the start of new AED era. At the end of 1995, a total of 8 new AEDs were introduced to the market with three of them being approved for clinical use in Korea (table 1). In addition, more than a dozen of new potential AEDs are in the process of preclinical investigations.

After a long latency period, we are suddenly facing a dynamic era of new AEDs. New AEDs have novel structures different from conventional AEDs (Fig. 1) and they have many favorable characteristics compared with old previous AEDs (table 2). The development of many new AEDs was based on logical considerations on the mechanisms of action. They have been extensively screened in animal expriments and passed through the rigorous clinical trials to prove its clinical efficacy in refractory epileptic pa-

Table 1. Approval of New AEDs

New AEDs	First Approval	Approval in Korea
Vigabatrin	1989, UK	1992
Zonisamide	1989, Japan	1992
Oxcarbazepin	1990, Denmark	—
Felbamate	1993, US	—
Lamotrigine	1994, US & UK	1995
Gabapentin	1994, US	preparing trial
Topiramate	1995, UK	under trial
Tiagabine	1995, UK	—

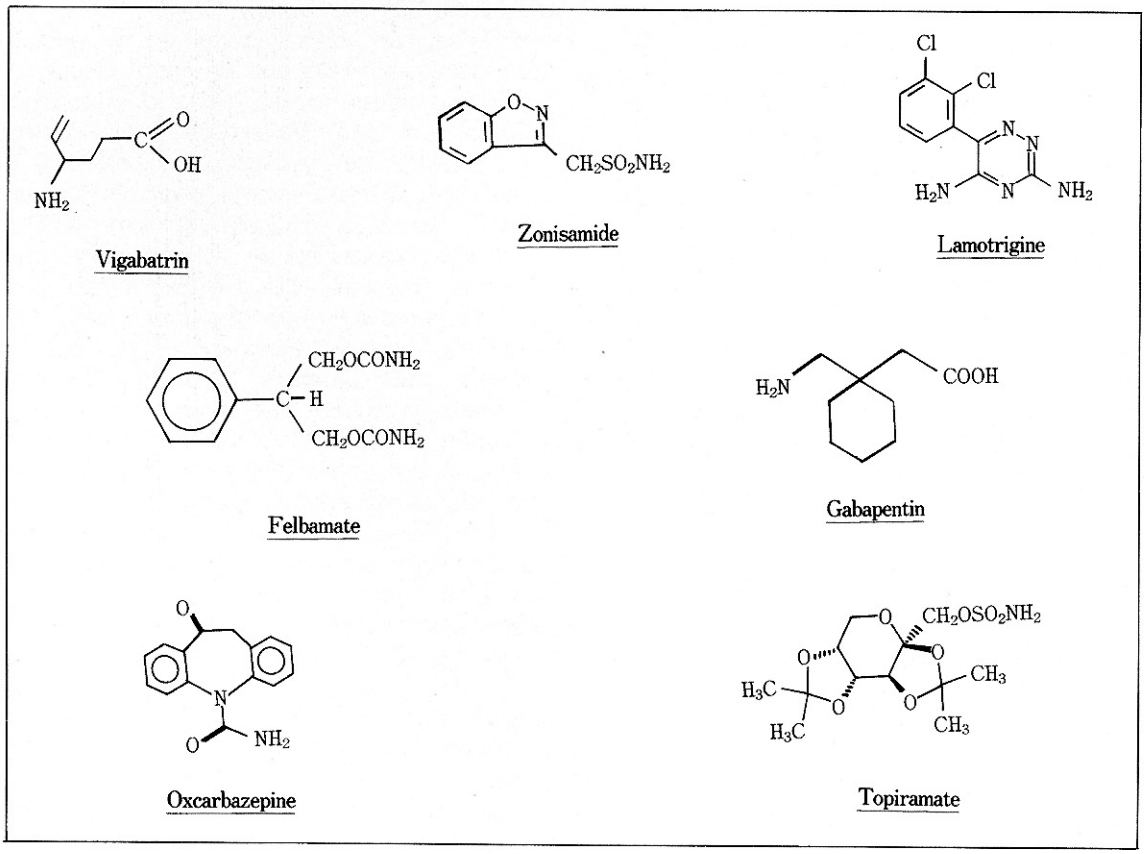

Fig. 1. Structures of New AEDs.

Table 2. General Characteristics of AEDs

	Conventional	New
Development	model oriented	mechanism oriented
Pharmacokinetics		
dose-conc. cuve	non-linear	linear
protein binding	high	none or low
metabolisim by hepatic Cyt P-450 enzyme	yes	none or in minor degree
drug interaction	high	low
Premarketing trials	minimal	extensive
Cost	low	high

tients. Their pharmacokinetic profiles and safety measures seem superior to conventional AEDs. It is quite likely that these new AEDs will not only greately improve the quality of drug management but also our insight on the pathogenesis of epileptogenesis.

From the viewpoint of epilepsy caring physicians, this is clearly an era of great excitement, however, the number of AEDs to choose has become suddenly too many to cause a serious confusion. In addition, all clinical trials of new AEDs were focused on the refractory partial epilepsy with very comparable efficacy and safety measures. It seems quite prudent to conduct a critical analysis of cummulated clinical experiences of these new AEDs not only to choose the most approprtate AED but also to conduct a careful postmarketing clinical surveilences to help our patients.

1. Development and Animal Experiments of New AEDs

A. Vigabatrin (r-vinyl GABA : VGB)

VGB is a GABA analogue which is an irreversible inhibitor of GABA transaminase, a GABA degrading enzyme. VGB was first synthesized by Jung et al of Marion Merrel Dow Laboratory in 1975 and was first tried in human epilepsy in 1982 for the purpose of potentiating inhibition by increasing synaptosomal GABA concentration. VGB was quite effective in audiogenic seizures in mice and photically induced sizures in baboon (papio papio). In chemically induced seizures, VGB was effective against strychnine and isoniazid induced seizures and the myoclonus induced by mucimol. VGB protected seizures induced by a low dose of bicuculline (0.55mg/kg) but not effective to a high dose of bicuculline (1.5-3 mg/kg) (*Jung and Palfreyman, 1995*).

Seizures induced by pentylentetrazole (PTZ)or picrotoxin (PCT) as well as maximal electric shock (MES) were not protected by VGB but microinjection of VGB into midbrain was effective. VGB was not clearly effective in amygdala-kindled seizures and aggravated absence seizures in rats. However, Shin et al.(1986) demonstrated anti-seizure and anti-epileptogenic effect of VGB in amygdaloid-kindling in rats.

Early animal toxicology studies of VGB showed impressive myelin changes consisted of intra-period splitting of myelin lamella in the brain of rats and dogs. However, this effect has not been observed in chronically treated monkeys. Extensive clinical trials and pathological studies did not demonstrate any evidence of myelin damage in humans (*Fisher and Kerrigan III, 1995*).

B. Zonisamide (3-sulfamoylmethyl-1, 2-benzisoxazole : ZNS)

ZNS was developed by Uno et al of Dainippon Laboratory in 1970s and was found to have anti-epileptic action during the process of routine biological testing of synthetic 1, 2-benzisoxazole derivatives.

ZNS, like PHT and CBZ, was effective to prevent hindlimb extension induced by MES, and restricted the focal seizure spread by electrical stimmulation of visual cortex. ZNS was also effective in suppressing the focal epileptogenic activities such as spikes induced by cortical freezing, cortical application of tungstic acid gel or conjugated estrogen. ZNS was also effective against seizure in kindled animals. These findings suggested that ZNS shares same mechanism of action with PHT and CBZ in one way and with VPA in another way (*Seino et al., 1995*).

C. Lamotrigine (6-<2, 3>-dichlorophenyl-1, 2, 3-triazine-3, 5 diamine : LTG)

LTG was developed by Wellcome Research Laboratory in 1970's in a rational approach to discover new AEDs based on the observations that many existing AEDs were antifolate. However, the antifolate activity of LTG was found to be very weak and there was no correlation between anticonvulsant activity and inhibition of dihydrofolate reductase.

LTG, like PHT and CBZ, blocks hindlimb extension following MES and PTZ, LTG was ineffective against PTZ induced clonus but was active against the photically evoked afterdischarge test. The contradictory results in these absence seizure models clearly demonstrate the limited usefulnes of animal models. LTG did not block the development of kindling but dramatically reduced the number of kindling seizures as well as the afterdischarge duration (*Goa et al : 1993*).

D. Felbamate (2-phenyl-1, 3 propanediol dicarbamate : FBM)

FBM was synthesized by Wallace Laboratory in 1954 and was screened by Antiepileptic Drug Development (ADD) program of NIH in 1982. FBM demonstrated anticonvulsant effects on MES and PTZ induced hind limb extensions and was also effective in increasing the seizure threshold of PTZ induced clonus. In these animal experiments FBM was found to have a high degree of safety as measured by neurototicity and calculated protective indices (PI : TD_{50}/ED_{50}). In rat, the oral ED_{50} was 238.1mg/kg and TD_{50} was estimated at > 3.000 mg/kg.

FBM was also effective against PCR and bicuculline induced seizures and seizures induced by intraventricular administration of NMDA. Also, seizures induced by glutamate, isoniazid, yohimbine, and 4-aminopyridine have beeen protected by FBM. In kindling models of epilepsy, FBM significantly elevated seizure threshold but failed to reduce afterdischarge duration in kindled rats. FBM was not effective against seizures induced by cobalt and strychnine (*Sofia, 1995*).

E. Gabapentin (<1-aminomethyl>-cyclohexaneacetic acid : GBP)

GBP was synthesized in Park-Davis Laboratory as a structural analogue of GABA and was first studied in the mid-1970s as an anti-spastic agent because of its structural similarity to the anti-spastic drug baclofen. Early animal experiments, however, demonstrated that its anti-convulsant effects were more significant. GBP was also effective in audiogenic seizures in mice and hippocampal kindling model in rats. GBP was not effetctive against NMDA or kainate induced tonic seizures, absence seizure model (wistar rat), and the photogenic myoclonus in papio papio (*Taylor, 1995*).

A statistically significant increase in the incidence of pancreatic acinar cell tumors was found in male Wistar rats receiving high dose of GBP (2,000 mg/kg), which were low grade malignancies, did not metastasize, and did not affect survival. The rat is not a generally accepted model for human pancreatic cancer and no pancreatic tumors have been reported in patients taking GBP (*Ramsay, 1995*).

F. Oxcarbazepine (10, 11-dihydro-10-OXO-carbamazepine : OXC)

OXC is a chemically related follow-up compound of CBZ developed by Ciba-Geigy Laboratory and has a similar therapeutic profile but improved tolerability. In animal experiments, OXC, like CBZ, was quite effective against the hindlimb extension seizures induced by MES and PTZ but ineffective against threshold clonus seizures induced by chemicals (*Dam and Østergaard, 1995*).

G. Topiramate (2, 3 : 4. 5-bis-o-<1-methylethylidine > B-D-fructopyranose sulfamate : TPM)

TPM is a novel AED first synthesized and identified in RW Johnson Laboratory in 1980. The first human epileptic patient was treated in 1986.

TPM was highly effective in blocking sizures induced by MES but not seizures induced by PTZ, PCR, or bicuculline (*Reife, 1994*).

The efficacy data of new AEDs in animal models are surmmarized in table 3. In general agents effective against MES induced hindlimb tonic extensor seizures are effective against partial and secondarily generalized seizures and the agents elevating the threshold of clonus seizures induced by PTZ and other chemicals are effective against absence seizures. Kindling is a model of complex partial seizures. In this regard, most new AEDs are effective for partial seizures and secondarily generalized tonic-clonic sei-

Table 3. Efficacy of AEDs in Animal Models

	MES	PTZ	PIC	STR	BIC	Kindling
CBZ	+	−	−	±	−	+
PHT	+	−	−	±	−	±
VPA	+	+	+	+	+	+
PB	+	+	+	+	+	+
ESM	−	+	+	±	±	−
BDZ	±	+	+	−	+	+
VGB	±	−	−	+	±	±
ZNS	+	−	−	−	−	+
LTG	+	−	−	−	−	+
FBM	+	+	+	−	±	+
GBP	+	+	−	−	−	+
OXC	+	−	−	±	−	+
TPX	+	−	−	−	−	?

* modified from Ramsay(1993).
• MES : maximal electric shock, • PTZ : pentylenetetrazol, • PIC : picrotoxin, • STR : strychnine, • BIC : bicuculline

zures. FBM and GBP seemed also effective for absence seizures.

2. Mechanisms of Action of New AEDs

Although considrable research efforts have been undertaken recently, our knowledge about the mechanisms of action of AEDs are still far from clear. In those cases in which drug mechanisms are reasonably well understood, three general themes of antiepileptic actions have been proposed. (*Rogawski and porter, 1990*) ; (a) modulation of voltage-dependent ion channels involved in action potential propagation or burst generation, (b) enhancement of GABA-mediated inhibition, and (c) suppression of acidic amino acid mediated excitation. Table 4 summarized the mechanisms of action of each AEDs.

A. AEDs modulating voltage-dependent ion channels.

1) blocking of Na-channels

Among conventional AEDs, PHT, CBZ and VPA effectively attenuate the post tetanic potentiation (PTP) in mammalian central neurons in tissue culture at their relevant concentrations (*McLean and Mcdonald, 1983*) which was the consequence of binding to Na^+ channel in unique voltage-and frequency-dependent manner.

For PHT, this is the most clearly documented action mechanism, however, CBZ and VPA may have additional or probable multiple mechanisms. Among new AEDs, ZNS, LTG and TPM have been shown to have similar Na^+ channel blocking effect as PHT. However, these new AEDs were found to have either additional different action mechanisms or have efficacy in different spectrum of seizures from PHT. LTG has also been shown to decrease the release of veratridine-

Table 4. Summary of Action Mechanisms of AEDs

1. Voltage-dependen tion channels
   i) voltage-dependent Na^+ channel
      PHT, CBZ, VPA, ZNS, LTG, FBM, OXC, TPM
   ii) T-type Ca^{++} channels
      ESM, VPA(±), ZNS
2. GABAergic potentiation
   i) modulation of $GABA_A$-Cl-channel complex
      PB, BDZ, TPM
   ii) increase of GABA synthesis
      THIP*, Progabide*
   iii) inhibition of GABA metabolism
      VGB, GBP(?), VPA(?)
   iv) increase of GABA release :
      nonavailable
   v) inhibition of GABA reuptake
      TIA
3. Suppression of acidic amino acid mediated excitation
   i) decrease of glutamate synthesis
      GBP(?), VGB(?)
   ii) NMDA receptor antagonist
      FBM, remacemide
   iii) non-NMDA receptor antagonist
      TPM
4. Unknown
      GBP, VPA

*was not effective in clinical trials.
Underlines indicate new AEDs

stimulated release of glutamate from rat cortical slices, which might account for its anticonvulsant action, but this appears contradictory in that tetrodotoxin(TTX) also blocks veratridine-induced glutamate release, but obviously has no anticonvulsant activities. Recently different types of voltage-operated sodium channels have been described which may have different pharmacological and functional characteristics. GBP also attenuate the PTP in central neurons, however, the effect is delayed by about 2 hours after addition of the drug, which suggest the indirect effect of GBP on Na^{+}-channel (*Davies, 1995*).

2) voltage-dependent calcium channels

Many AEDs like PHT, PB and BDZ reduce calcium influx into synaptic terminals and block presynaptic release of neurotransmitters. However, these actions have been demonstrated only at high drug concentrations which might not be clinically relevant. Among conventional AEDs, ESM has been clearly demonstrated to block T-type calcium channels in acutely dissociated neurons from the rat thalamas (*Coulter et al., 1989*), which is important for the generation of 3Hz SWC in absence seizures. VPA was also shown to reduce T-type Ca^{++} currents in primary afferent neurons (*Kelly et al., 1990*). However, the effect was modest and its effect on T-type Ca^{++} channels in thalamic neurons has not been demonstrated.

ZNS was also found to reduce T-type Ca^{++} current without affecting L-type Ca^{++} currents in cultured neurons of rat embryo cerebral corteces in a concentation-related manner (Suzuki et al., 1992) which may contribute to its efficacy in generalized epilepsies.

B. AEDs Potentiating GABAergic Inhibition

GABA is the major inhibitory transmitter throughout the neuroaxis. The vast majority of interneurones in the cerebral cortex are GABAergic which play an important part in controlling glutamate-mediated excitatory activity within the cortex. There are two subtypes of GABA receptors, designated $GABA_A$ and $GABA_B$. The $GABA_A$ receptors are located predominantly on postsynaptic membranes and are involved in fast neurotransmission. It is part of the transmitter-gated channel which consists of five membrane-spanning subunits($\alpha, \beta, \gamma, \delta$ and ρ) that form the pore through which chloride ions enter the postsynaptic neurons. Each subunit of $GABA_A$ receptor has many isoforms and, consequently of different pentameric combinations of subunits, raises many different types of $GABA_A$ receptor with various physiological characteristics. $GABA_B$ receptors are found both pre-and post-synaptically and are linked to GTP binding proteins. Depending on the cellular location of these receptors, activation can lead to either anti-or pro-convulsant.

The potentiation of GABAergic inhibition can be achieved by many different ways.

1) modulation of $GABA_A$-Cl-channel complex

BDZ and PB binds to their specific allosteric regulatory site on the receptor to enhance the $GABA_A$ receptor current. BDZ increases $GABA_A$ receptor opening frequency but PB increases mean channel opening duration. TPM at therapeutic concentration increased GABA-induced Cl-fluxes in cultured cerebellar and cortical neurons. However, TPM does not interact with BDZ binding site on $GABA_A$ receptors. Therefore, it is likely that TPM is acting on a $GABA_A$ receptor subtype that is not modulated by BDZ (*Reife, 1994*).

2) increase the synthesis of GABA

VPA is believed to increase the synthesis of GABA by increasing the activity of glutamic acid decarboxylase but at higher concentration which is not clinically relevant. Unfortunately GABA itself cannot therapeutically administered because it does not cross the blood-brain-barrier. Use of a prodrug or GABA agonist would be a rational approach which has been attempted with 4, 5, 6, 7-tetrahydro isoxazolo-5,4,-C-pyridine-3-ol(THIP) and progabide. However, both agents yielded dissapointing results in clinical trials.

3) inhibition of metabolism of GABA

VPA can inhibit GABA transaminase but not at therapeutically relevant doses. VGB is an irreversible inhibitor of GABA-T and was found to increase cerebral GABA concentration which has correlated with its therapeutic efficacy on epilepsy.

4) increase the release of GABA into the synaptic cleft

To date, no therapeutic agent has been produced that acts via this potential mechanism.

5) inhibition of GABA uptake

GABA released into the synapse is inactivated by high affinity uptake systems that transport synaptic GABA into neurons and glial cells. Tiagabin (TIA), a new AED under trial, exerts antiepileptic activity by

specifically inhibiting this uptake of GABA from the synaptic cleft, which apparently prolong the physiologic effect of GABA.

C. AEDs suppressing acidic amino-acid mediated excitation

Glutamate and aspartate have long been known to excite neurons and cause convulsive activity when applied to the cerebral cortex and the cellular mechanisms underlying these actions have been clarified in 1980s. The excitatory amino acid receptors are classified into AMPA, Kainate, and NMDA receptors which are coupled to a cation channel. Among those subtypes NMDA receptor plays a critical role in many types of seizures ; activation of NMDA receptors in in-vitro hippocampal slices leads to burst firing reminiscent of epileptiform discharges recorded in various seizure models and selective NMDA receptor antagonists are anticonvulsant in many seizure models (*Rogawski and Porter, 1990*).

1) decreased synthesis or release of excitatory amino acids

Most AEDs acting on voltage-dependent Na^+ channels like LTG are known to presynaptically decrease the release of excitatory amino acids : glutamate and aspartate, which might be relevant to their mechanisms of action in certain degree. Recently in-vivo Magnetic Spectroscopic Measurements of cerebral amino acid in humans taking VGB demonstrated significant elevation of glutamine and reduction of glutamate concentration which raised the possibility of VGB altering the glutamate/glutamine cycle in human CNS (*Petroff et al., 1994*).

Decreased synthesis of glutamate was also postulated as one mechanism of GBP which requires a further confirmation (*Taylor, 1994*).

2) NMDA receptor antagonist

NMDA receptor comprised recognition domains for glutamate and several endogenous co-agonists, and modulatory subtances including glycine and polyamines. The receptor also contains a cation-selective pore that serves as a pathway across the neuronal membrane for Na^+, K^+ and Ca^{++} ions. In animal experiments NMDA receptor antagonists were not only protective against the generalized tonic seizures and partial seizures but also featured a powerful protection against the induction of kindled seizures suggesting that NMDA receptor antagonists confer antiepileptogenic activities. There are several approaches for inhibiting NMDA receptor function, including targeting of the NMDA, glycine, and polyamine recognition sites. In addition, there has been some interesting drugs that block the NMDA receptor channel (non-competitive antagonists) which requires the receptor channel to be gated in the open state for their binding to exert blocking action. This channel blocking NMDA antagonists fall into two broad categories : dissociative anesthetic-like agents and low affinity antagonists. Dissociative anesthetics exert a potent broad spectrum anticonvulsant action, however, they produce severe neurobehavioral side effects and reversible microvacuolation in rat cortical neurons. On the other hand low affinity channel blockers demonstrated an acceptable level of safety.

Among new AEDs, remacemide hydrochloride which is under clinical trials is belong to the low affinity NMDA receptor-channel blockers. Remacemide hydrochloride and its active metabolite, ARL_{12495}, have additional effect on voltage-dependent Na^+-channels. The specific site of FBM action is not known, but an important site appears to be the strychnine-insensitive glycine recegnition site of NMDA receptor which was supported by the inhibition of $[^3H]$-5, 7-dichloro kyurenic acid (a high-affinity glycine receptor antagonist) binding by FBM (*McCabe et al., 1993*). FBM was also found to potentiate GABAergic ation (Rho et al., 1994), however, only at high concentrations that are probably not clinically meaningful. Recently FBM was shown to effectively block sustained repetitive firing in mouse spinal cord neurons grown in tissue culture suggesting actions on voltage dependent sodium channels like PHT (White et al., 1995).

3) non-NMDA receptor antagonist

The anticonvulsant efficacy of non-NMDA receptor antagonists has not been fully investigated yet. However, AMPA receptor antagonists (NBQX, GYKI 52466) are anticonvulsant in reflex models of epilepsy. TPM was shown to antagonize the ability of kainate to activate kainate/AMPA subtype of glutamate receptor, but had no apparent effect on the activity of NMDA receptor. Apparently TPM has additional actions on voltage-dependent Na- channels and $GABA_A$ receptor-Cl-channel complexes which makes the significance of non-NMDA receptor antagonist unclear.

D. AEDs whose mechanism of action is unresolved

1) Among conventional AEDs, the action mechanisms of VPA has not been fully elucidated although inhibition of rapid sustained repetitive discharges has been demonstrated. It is likely that VPA has additional multiple other mechanisms.

2) GBP, a new AED, was originally synthesized as an analogue of GABA but it does not posses high affinity for either $GABA_A$ or $GABA_B$ receptors. GBP has been shown binding to a novel high affinity site in the CNS and to be displaced by the anticonvulsant 3-isobutyl GABA. This site is linked to the transporter for large neutral L-amino acids; L-methionine, L-leucine, and L-isoleucine. These amino acids also potently displace GBP from its binding site. GBP interacts with at least three cytosolic enzymes involved with amino acid metabolism; it inhibits branched-chain aminotransferase, which converts L-leucine, L-isoleucine, and L-valine into glutamate; it enhances the action of glutamate dehydrogenase which catalyzes both the degradation and synthesis of glutamate under appropriate conditions; it is also a weak inhibitor of GABA-transaminase, which degrades GABA into other amino acid. Measurement of in-vivo brain GABA concentration by ^1H magnetic resonance spectroscpy indicated highter brain GABA level in patients taking higher dose of GBP than the standard dose (*Petroff et al., 1996*). These findings suggest that the anticonvulsant action of GBP may result from alteration in the concentration or metabolism of brain amino acids (*Taylor, 1994*).

3. Pharmacokinetics and Drug Interaction

The parmacokinetic profile of an "ideal" AED would include complete bioavailability with slow absorption, availability of a parenteral formulation, a single-compartment volume of distribution, low and non-saturable protein binding, elimination half life of about 24hr, linear elimination kinetics, no autoinduction of enzymatic biotrans-formation, no active metabolites, and no pharmacokinetic interactions with other drugs. Unfortunately, none of the current or new AEDs combines all of these attributes.

Pharmacokinetic profiles of new AEDs are summarized in table 5.

A. Bioavalability

all new-AEDs have good bioavailablity after oral administration except GBP. The bioavailability of GBP is inversely dose related : the bioavailability of a 300 mg oral dose is about 60 % compared with 35 % for a 1600mg oral dose. This may be related to the characteristics of L-transporter system.

Table 5. Pharmacokinetics of New AEDs

	VGB	ZSM	LTG	FBM	GBP	OCBZ	TPM
Bioavailability(%)	>80	~100	~95	~85	40-60	~100	>80
Tmax*(hrs)*	1-2	2-5	4-12	6-20	2-3	4-6(MHD)	1-4
Dose-concentration kinetics	linear	linear	linear	linear	linear	linear	linear
Vd*(L/kg)*	0.8	1.2-1.8	1.1	0.8	1.0	0.7-0.8	0.8
Protein bound(%)	0	50-60	55	25-35 (22-25 %)	0	OCBZ : 60 MHD : 40	15
Hepatic metabolism	none	conjugation hydroxyilation	conjugation	hydroxylation followed by conjugation	none	reduction glucuronidation	hydroxylation
Active metabolites	none	none	none	none	none	MHD	none
Autoinduction	none	none	yes	none	none	none	none
$T^1/_2$*(h)*	5-7 (not relevent)	60	24	19	5-9	OCBZ : 1-2 MHD : 8-10	20-30
Induction of hepatic cytochrome P450 system	-	-	-	+	-	-	-
Route of excretion	renal	renal	renal	renal	renal	renal	renal
% unchanged in Urine	100	29-48	10	40-50	100	OCBZ : 1 MHPD : 27	85 %

B. Parenteral form

None of new AEDs have parenteral form available yet.

C. Metabolism and excretion

VGB and GBP are not metabolized and entirely eliminated by renal excretion, thus they are pharmacokinetically clean.

Other new AEDs are metabolized in liver and subjected to drug interactions. ZNS is metabolised in the liver through multiple pathways employing direct acetyl or glucuronyl conjugation, hydroxylation followed by oxidation, and hydroxylation followed by conjugation. However, ZNS did not exhibit inducing/inhibitory effects on the hepatic microsomal enzyme systems. Neither active metabolites nor autoinduction has been observed. About 85 % of ZNS administered is excreted in the urine and 15 % in the feces. Unchanged form comprises about 29-48 % of ZNS metabolites recovered in the urine.

LTG is extensively metabolized in humans by Uridine 5'-diphosphate (UDP)-glucuronosyl-transferases with its major metabolite being identified as N-2 glucuronide conjugate. No active metabolites were identified. LTG induces its own metabolism, resulting in a 25 % decrease in the elimination half-life at steady state. However, this occurs early before reaching steady state and not thought to be clinically significant. Renal excretion ($\geq$ 90 %) is the major route of LTG elimination. 2-N glucuronide conjugate form comprises 75 to 90 % of urinary excretion and 10 % is recovered in the urine as unchanged form.

FBM is metabolized in the liver by initial hydroxylation followed by conjugation or initial hydrolysis followed by oxidation. No active metabolites have been identified but FBM was found to be a mild hepatic cytochrome P450 inducer. Renal excretion ($\geq$ 90 %) is the major route of FBM elimination and 40 to 50 % is excreted as unchanged form.

OXC is pharmacokinetically quite unique in that absorbed OXC is rapidly and extensively metabolized to the active metabolite, MHD, by cytosol arylketone reductase ; The AUC(0-72hr) of OXC amounted to 1 % to 2 % of the AUC for MHD. Both OXC and MHD are further metabolized into glucuronide conjugate.

TPM is not extensively metabolized, its metabolism is inducible but there is no evidence of autoinduction. TPM is primarily metabolized by hydroxylation or hydrolysis of the isopropylidene group. Only about 15 to 20 % of TPM is metabolized after a single dose in healthy adults, but up to 50 % of the administered dose is metabolized under multiple dosing conditions in patients treated with other inducing AEDs. The elimination of TPM is predominantly renal, with 50 to 85 % of the dose excreted as unchanged form.

D. Elimination half-life

A drug's half-life has practical relevance as it determines the optimal dosing interval, the time to steady-state, and the washout period after drug discontinuation. However, it is important to note that a drug's pharmacokinetic half-life is not necessarily the same as its pharmacodynamic half-life. Most new AEDs have adequate half-life(=24hr) with a few exceptions.

The half-life of VGB is 7-8 hr. However, pharmacodynamic half-life of VGB is much longer because of its mechanism of action : irreversible inhibition of GABA-T. It takes several days for GABA-T to return to control levels after a single VGB dose. Therefore, the pharmcokinetic half-life bears no relationship to the duration of the drug's pharmacodynamic effects.

The half-life of ZNS is 63-68hr in healthy volunteers or patients under ZNS monotherapy. However, half-life of ZNS was significantly decreased in patients on monotherapy with PHT(27.1hr), CBZ(36.4hr), or on polytherapy(28.4hr).

The half life of LTG is 24hr in healthy volunteers, however, the rate of elimination of LTG is increased substantially in patients receiving inducing AEDs(CBZ, PB, PHT, PRM) with the reduction of half-life to 14 to 15hr. On the other hand, VPA inhibit the elimination of LTG to increase half-life to about 60hr, probably due to competition between VPA and LTG for hepatic glucuronidation. In patients taking both inducing AEDs and VPA, their respective effects appear to be cancelled out and LTG half-life is similar to those found in healthy volunteers.

Mean elimination half-life of FBM ranged from 16 to 22hr regardless of dose. The half-life of FBM decreased to 14.6hr in patients taking CBZ. VPA appears to have only minimal effects on FBM half-life (=22hr).

The half-life of OXC is only 1-2hr and MHD is 8 to 10hr. The half-life of TPM is 21hr and pretreatment with PHT or CBZ decreases the half-life of TPM significantly by a factor of 1.5 to 2. However, VPA has no significant effect on serum TPM levels.

E. Interactions with other AEDs

1) effects of new AEDs on other AEDs

In general the pharmacokinetic interactions of new AEDs are significantly less than conventional AEDs with an exception of FBM.

Theoretically, non-metabolising AEDs, VGB and GBP, should not have any significant interactions with other AEDs. However, clinical trials of VGB have shown to decrease plasma concentration of PHT by 20 %. The mechanism is not still clear but it has been suggested that VGB may cause an increase in tissue binding sites for PHT to increase its volume of distribution (*Rimmer and Richens, 1989*).

Clinical trials of ZNS, LTG, GBP, OCX, and TPM did not show any significant alterations on the plasma level of previously taking conventional AEDs. Several investigators have observed increased incidence of cerebellar toxicities in patients taking both LTG and CBZ and reported increased plasma concentration of CBZ-epoxide. However, subsequent investigations did not disclose any significant alterations in the plasma level of CBZ-epoxide (*Besag et al., 1994*).

FBM increase plasma concentration of PHT in a dose dependent manner due to its competitive inhibition on PHT metabolizing enzyme (CYP 2C9 and CYP 2C19). Therefore, it is recommended to decrease the dose of PHT by 20 % at starting FBM. With increasing dose of FBM, further reduction of PHT dose is required according to the patient's condition. FBM decrease the plasma concentration of CBZ by 30 % but increase the concentration of CBZ-epoxide by 57 % due to induction of CBZ metabolism. The effect of FBM on VPA was similar to PHT with dose dependent increase of VPA concentration suggesting an effect on valproate glucuronidation or on P450-mediated pathways.

The overall effect of new AEDs on conventional AEDs are summarized in table 6.

2) effects of conventional AEDs on new AEDs

This has been already described in the section of elimination half-life of new AEDs and summarized in table 7.

Table 6. Effect of New AEDs on Conventional AEDs

	CBZ	PHT	PB	VPA
VGB	none	↓ 20 %	none	none
ZNS	none	none	none	none
LTG	none	none	none	none
FBM	↓ 24-53 % ↑ CBZ-epoxide	↑ 20-50 %	?	↑ 24-53 %
GBP	none	none	none	none
OCBZ	none	none	none	none
TP	none	none	none	none

In general, non-metabolizing new AEDs (VGB and GBP) were not affected by conventional AEDs. However, enzyme inducing AEDs significantly increase the clearance of other new AEDs. On the other hand, the effect of VPA(an enzyme inhibiting AED) was most prominent on LTG but was negligible on other new AEDs.

3) interactions with other drugs

VGB and GBP are not expected interact with other drugs because of their non-metabolizing characteristics and absence of protein binding. LTG is metabolized mainly by glucuronidation and therefore drugs that are also eliminated via this pathway might be exected to have interactions with LTG. Paracetamol(acetaminophen) was shown to increase the rate of total body clearence of LTG by 15 %. Any significant effects of LTG on oral contraceptive pill have not been found.

Drug interactions with other new AEDs have not been fully investigated yet.

Although OXC exerts less liver enzyme induction than does CBZ, OXC interact with oral contraceptives to increase the incidence of breakthrough bleeding (*Klosterskov Jensen et al., 1992*). OXC also decrease the concentration of felodipine, a calcium antagonist, however, there was no interaction with oral anticoagulant warfarin. Verapamil was shown to decrease the concentration of MHD but not OXC. The interactions of ZNS, FBM and TPM with other drugs have not been fully investigated yet.

Table 7. Effect of Conventional AEDs on New AEDs (Serum level)

	VGB	ZSM	LTG	FBM	GBP	OCBZ	TPM
CBZ	none	↓ 30-40 %	↓ 40-50 %	↓ 40 %	none	?	↓ 50 %
PHT	none	↓ 40 %	↓ 40-50 %	↓ 45 %	none	?	↓ 50 %
PB	none	↓ ?	↓ 40-50 %	↓ ?	none	none	↓ ?
VPA	none	none	↑ 100 %	none	none	none	↓ 13 %

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