The new anti-epileptic drugs: A clinical profile

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ABSTRACT

Over the past few years, a number of new anti-epileptic drugs have been introduced including: gabapentin, lamotrigine, vigabatrin, topiramate, felbamate and tiagabine. Several clinical studies showed efficacy of these anti-epileptic drugs on various types of seizures. However, the pharmacologic and clinical properties of these drugs remain to be fully defined. In this review, the pharmacokinetics, indications, and side-effects of the new anti-epileptic drugs are summarized.

Keywords: Epilepsy, anti-epileptic drugs, pharmacokinetics.


The principle aim in the treatment of the epilepsies is control of various seizures. This traditionally has been achieved by conventional anti-epileptic drugs (AEDs) such as phenytoin, carbamazepine, valproic acid, ethosuximide and phenobarbitalone. These medications control seizures in 70% of treated patients. The continued quest for better seizure control has resulted in the rapid emergence of the new anti-epileptic drugs including gabapentin, lamotrigine, vigabatrin, topiramate, felbamate, and tiagabine. Although these anti-epileptic drugs have already been used in the United States, Europe and Japan, only three are available in the Kingdom including gabapentin, lamotrigine and vigabatrin. Some enterprising patients may bring these medications from elsewhere for use. Therefore a review of the new AED's pharmacology, pharmacokinetics, indications, and side-effects is needed. The aim of this article is to review the current understanding of the various aspects of the new AEDs.

Factors limiting full understanding of the new anti-epileptic drugs. Several factors interfere with the proper understanding of the various aspects of the new AEDs. These factors stem from the fact that the new AEDs have been tested mainly as an add-on therapy in patients with refractory seizures who fail to respond to conventional anti-epileptic therapies. These commonly included partial seizures with or without secondary generalization and other specific syndromes e.g. Lennox-Gastaut syndrome. These new AEDs have also been tested in the medication withdrawal period, prior to epilepsy surgery. This has resulted in several limitations including selection bias, unknown efficacy on idiopathic epilepsies, difficulty in establishing the optimal dose for individual anti-epileptic drugs, difficulty in establishing the specific side-effects profile for individual anti-epileptic drugs, obscuration of rare and long term side-effects for the new AEDs. In addition, this has raised the question concerning the validity and merits of comparing the new AEDs with conventional ones. Time and experience will provide the definitive answer, but some experience has already been accumulated to warrant a specific statement.

The new anti-epileptic drugs. Gabapentin. Gabapentin (Neurontin, Parke Davis) is a structural
analogue of gamma-aminobutyric acid (GABA)\(^8\) which may increase the total central nervous system level of GABA.\(^9\) Its exact mechanism of action remains uncertain despite the finding that gabapentin appears not to act on the gabanergic system, but on a previously unknown receptor that is distinct from the gabanergic-receptor system.\(^10\) It has been shown to be effective in complex partial seizures with or without secondary generalization\(^11-13\) as well as generalized tonic-clonic seizures. On the other hand, it has been shown to have no significant effect compared to placebo in reducing the frequency of myoclonic seizures or absences.\(^14\) Gabapentin is well absorbed following an oral dose and is not protein bound or metabolized in the liver and has a half life of 6 hours. The commonest side-effects are fatigue, dizziness and weight gain which seem to be dose related.\(^15\) The drug has no reported interactions with other anti-epileptic drugs. Table 1 depicts some of the features of gabapentin.

**Lamotrigine.** Lamotrigine (Lamictal, Glaxo-Wellcome) acts by inhibiting the release of excitatory amino-acids such as glutamate through the modulation of sodium.\(^16\) Its half life is approximately 24 hours.\(^17\) Lamotrigine has been found to be effective as an add-on and mono therapy for patients with partial seizures with or without secondary generalization.\(^18,19\) In addition, lamotrigine has also been effective in the treatment of absences, myoclonic seizures, and seizures associated with Lennox-Gastaut syndrome.\(^20,21\) Lamotrigine is partially protein bound and undergoes liver metabolism by glucoronidation.\(^22\) Therefore, it has significant drug interactions with valproic acid,

Table 1 - Overview of the new anti-epileptic drugs.

<table>
<thead>
<tr>
<th>Name</th>
<th>Indications</th>
<th>Dose</th>
<th>Pharmacokinetics</th>
<th>Side Effects</th>
<th>Interactions</th>
<th>Mechanism of Action</th>
<th>Formulation</th>
<th>Mfr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Partial seizures</td>
<td>600-1,800 mg/d</td>
<td>Eliminated by kidney t(_1/2) = 6 hrs</td>
<td>Fatigue, Weight gain</td>
<td>None reported</td>
<td>Unknown: GABA analogue</td>
<td>Capsules: 100,300,400 mg</td>
<td>Parke-Davis</td>
</tr>
<tr>
<td>(Neurontin)</td>
<td>with or without</td>
<td>(in 3 divided doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25, 100, 150, 200, 300, 400 mg</td>
<td>Glaxo-Wellicome</td>
</tr>
<tr>
<td></td>
<td>generalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tablets: 500 mg</td>
<td>Marion Merrel Dow</td>
</tr>
<tr>
<td></td>
<td>T-C seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tablets: 25, 100, 200 mg</td>
<td>Ortho-McNiel</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Partial seizures</td>
<td>100-500 mg/d</td>
<td>Eliminated by liver t(_1/2) = 24 hrs</td>
<td>Hypersensitivity, especially in children</td>
<td>Increased VPA, Decreased CBZ, DPH, PB</td>
<td>Modulate voltage-gated sodium channels</td>
<td>Tablets: 400, 600 mg</td>
<td>Wallace</td>
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<tr>
<td>(Lamictal)</td>
<td>Generalized absence, myoclonic</td>
<td>(in 2 divided doses)</td>
<td></td>
<td></td>
<td></td>
<td>Inhibit excitatory neurotransmitter</td>
<td>Suspension: 600mg/5ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>release</td>
<td>Tablets: 4,12,16,20 mg</td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Partial seizures</td>
<td>500-3,000 mg/d</td>
<td>Eliminated by kidney t(_1/2) = 6 hrs</td>
<td>Sedation, Weight gain, Ataxia, Exacerbation of depression, Visual field constriction</td>
<td>Decreased DPH</td>
<td>Inhibit GABA transaminase</td>
<td>Tablets: 500 mg</td>
<td>Marion Merrel Dow</td>
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<tr>
<td>(Sabril)</td>
<td>Infantile spasms</td>
<td>(in 2 divided doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tablets: 25, 100, 200 mg</td>
<td>Ortho-McNiel</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Partial seizures</td>
<td>300-400 mg/d</td>
<td>Eliminated by kidney and liver t(_1/2) = 24 hrs</td>
<td>Fatigue, GI distress, Psychological disturbance, Weight loss, Renal calculi</td>
<td>Decreased CBZ, Increased DPH, Decreased PB</td>
<td>Inhibit voltage-gated sodium channels</td>
<td>Tablets: 400, 600 mg</td>
<td></td>
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<tr>
<td>(Topamax)</td>
<td>with or without</td>
<td>(in 2 divided doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suspension: 600mg/5ml</td>
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<td></td>
<td>secondary generalization</td>
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<td></td>
<td></td>
<td></td>
<td>Tablets: 4,12,16,20 mg</td>
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<tr>
<td>Felbamate</td>
<td>Partial seizures</td>
<td>1,200-3,600 mg/d</td>
<td>Eliminated by kidney t(_1/2) = 12-23 hrs</td>
<td>Headache, GI distress, Weight loss, Insomnia, Aplastic anemia, Liver failure</td>
<td>Increased VPA, Increased CBZ, DPH</td>
<td>Inhibit excitatory NMDA receptors</td>
<td>Tablets: 4,12,16,20 mg</td>
<td>Novo Nordisk-Abbott</td>
</tr>
<tr>
<td>(Felbatol)</td>
<td>Lennox-Gastaut</td>
<td>(3-4 divided doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25, 100, 200 mg</td>
<td></td>
</tr>
<tr>
<td>Tingabine</td>
<td>Partial seizures</td>
<td>32-56 mg</td>
<td>Eliminated by liver t(_1/2) = 6 hrs</td>
<td>Sedation, VPA, DPH, re-uptake</td>
<td></td>
<td>Inhibit GABA transaminase</td>
<td>Tablets: 4,12,16,20 mg</td>
<td>Novo Nordisk-Abbott</td>
</tr>
<tr>
<td>(Gabitril)</td>
<td></td>
<td>(in 2 to 4 divided doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25, 100, 200 mg</td>
<td></td>
</tr>
</tbody>
</table>

| CBZ = carbamazepine | NMDA = N-methyl-D-aspartate |
| DPH = diphenylhydantoin | Decr = decrease |
| GABA = gamma aminobutyric acid | Incre = increase |
| GI = gastro-intestinal | t\(_1/2\) = serum half life |
The new anti-epileptic drugs ... Al-Sulaiman

carbamazepine, phenytoin and phenobarbitone. When given in association with carbamazepine, phenytoin and phenobarbitone, lamotrigine $t_{1/2}$ is reduced to 12-14 hours. On the other hand when given with valproic acid its $t_{1/2}$ is 56-72 hours. The commonest side effect is hypersensitivity reaction particularly skin rash which occurs usually within 3 months of drug introduction. This complication particularly occurs in children. Slowly introducing the drug may overt such a complication.

**Vigabatrin.** Vigabatrin (Sabril, Marion Merrell Dow) is a synthetic GABA derivative causing irreversible inhibition of GABA transaminase. This results in blocking GABA breakdown, therefore increasing the pool of the inhibitory neurotransmitter. It is well-absorbed following an oral dose with the $t_{1/2}$ of 5 hours. However, because it is irreversibly inhibiting GABA transaminase its clinical action outlives its plasma $t_{1/2}$ allowing less frequent dosing. It is mainly eliminated by the kidneys unchanged. Vigabatrin is effective in patients with partial seizures. Some studies showed a favorable effect in patients with infantile spasms particularly those associated with tuberous sclerosis. The main side effects of vigabatrin include sedation, weight gain and at times ataxia. Vigabatrin has also been shown to exacerbate existing psychiatric problems, particularly depression. Visual field constriction and more recently, retinal cone system dysfunction have been described as a side effect particularly in the elderly. This complication appears to be related to the dose and duration of exposure.

**Topiramate.** Topiramate (Topamax, Ortho-McNeil) is a sulfamate-substituted monosaccharide with carboxy anhydrase inhibitory properties. Its mechanism of action as an anti-epileptic drug is unknown but may relate to a membrane-stabilizing activity. It is well absorbed following an oral dose. It exhibits minimal protein binding properties and is eliminated primarily by the kidneys and liver with a plasma $t_{1/2}$ of approximately 24 hours. Despite being eliminated primarily by the kidneys, the drug half life is markedly reduced when administered with enzyme-inducing drugs, particularly carbamazepine, phenytoin, and phenobarbitone. Topiramate is effective in patients with partial seizures and secondary generalized seizures who fail to respond to other drugs. The commonest side-effects include fatigue, gastro-intestinal distress, weight loss, insomnia, and most importantly hypersensitivity reaction particularly aplastic anemia and liver failure. Approximately a third of patients affected with aplastic anemia or liver failure die. This has lead to curtailed market activity of the drug.

**Tiagabine.** Tiagabine (Gabitril, Novo Nordisk) is a nipeptic acid derivative that exhibits anti-epileptic activity via inhibiting post-synaptic GABA re-uptake. Following an oral dose the drug is highly protein bound with elimination primarily occurring in the liver. The half life is approximately 6 hours. Tiagabine increases the serum levels of phenytoin and valproic acid. A number of controlled trials showed that tiagabine is effective as an adjuvant therapy in patients with partial seizures. The commonest side-effect of this drug is sedation.

The new anti-epileptic medications, women and pregnancy. The new AEDs hold a special promise for treatment of women with epilepsy. Most of these drugs particularly vigabatrin and gabapentin do not cause hepatic enzyme induction and hence avoids the risk of interaction with oral contraceptive pills. Lamotrigine, also, does not interact with oral contraception. In addition, these drugs have shown no teratogenic effects in laboratory animals. Further studies in this regard are warranted.

Other new anti-epileptic drugs. A number of other drugs including oxcarbazepine, a metabolite of carbamazepine, and fosphenytoin which is a phenytoin pro-drug have been widely used in Europe and in the United States. These drugs have not been introduced in the Kingdom. Other new anti-epileptic drugs include zonisamide which is used for partial seizures with or without secondary generalization as well as myoclonic epilepsy. The drug causes renal calculi in the western world and hence its use has been suspended. Similar side-effects were not seen in Japan.

In conclusion, several new anti-epileptic drugs have been shown to be effective in the treatment of various forms of epilepsy. Gabapentin and vigabatrin are well tolerated with minimal drug interaction and side-effects making them the first drugs of choice as an add-on therapy although the visual field constriction occurring with vigabatrin is concerning. Lamotrigine is well tolerated with minimal side-effects particularly when introduced in gradual doses, observing for hypersensitivity reaction particularly when administered with other AEDs. Topiramate use is limited by its psychological complications. Tiagabine use has been hampered by drug interactions.

References


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