Synthesis of Anti –epileptic Drug

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Abstract

In recent years, the number of commercially avail- able antiepileptic drugs (aeds) has increased steadily. This may make management decisions more difficult, but it also presents some welcome new options for efficiently individualising care. Opportunities to customise drug treatment to the unique patient's characteristics have never been stronger due to the fact that each of the available aeds differs from others in a number of therapeutically significant aspects. Spectrum of efficacy in various seizure types, adverse effects profile, pharmacokinetic properties, susceptibility to cause or be a target of clinically important drug-drug interactions, ease of use, and cost are all factors that should be taken into consideration when choosing a drug for patients with epilepsy. It is also important to take into account the accessibility of user-friendly paediatric formulations and any potential positive effects on co-morbid conditions when selecting a medicine. In fact, a number of aeds, notably those used to treat psychiatric disorders, prevent migraines, and treat neuropathic pain, are effective and frequently used for other purposes. Recent years have seen improvements in our understanding of the molecular mechanisms underlying the effects of drugs. Even if a fully mechanistic approach to the clinical use of these medications is not currently practical, understanding their mechanisms of action can help predict their efficacy profile and range of potential side effects.

Introductory Remarks

Since epilepsy affects 1% of the population, there is no doubt that it is one of the most common neurological conditions. The use of traditional antiepileptic medications can offer satisfactory seizure control for 75–80% of epileptic individuals. The most widely used traditional antiepileptic drugs include carbamazepine, ethosuximide, phenobarbital, phenytoin, and valproate. Nine novel antiepileptic medicines have so far been discovered and licenced, mostly as add-on treatments for patients who are not responding well to traditional therapy due to the therapeutic failure in 20–25% of patients. These include zonisamide, topiramate, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and tiagabine.

The majority of antiepileptic medications have many mechanisms of action. Based on these principles, Deckers has proposed classifying antiepileptic medications. Antiepileptic drugs, such as carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate, are in the first group. These drugs prevent sustained repetitive firing in individual neurons, with their effect primarily being caused by the blockade of voltage-dependent sodium or calcium channels. These medications can prevent both partial and generalised tonic-clonic seizures. The second category of medications consists of benzodiazepines, gabapentin, phenobarbital, tiagabine, topiramate, vigabatrin, and valproate, which enhance inhibitory actions mediated by g-aminobutyric acid (GABA). All seizure types (absence, generalised tonic-clonic, and partial seizures) may be treated with some of these medications. The third category essentially

consists of ethosuximide, a T-type calcium channel blocker that works against absences. Recent data suggests that zonisamide may possibly function as a calcium channel T-type inhibitor. A different class of medications may also be proposed; these antiepileptic medications lessen events caused by excitatory amino acids (glutamate), and as of right now, three antiepileptics fit this description: Topiramate, felbamate, and phenobarbital.

Antiepileptic Drugs And Gaba-Mediated Inhibition

In the early 1960s, valproic acid sodium salt was first used in the treatment of epilepsy. One of the most likely mechanisms underlying its anticonvulsant effects could be metabolic degradation inhibition, which would raise the level of GABA in the synaptic cleft. Data further show that there is no connection between the protective effects of valproate and a rise in GABA; in fact, valproate significantly reduced the seizure activity induced by the GABA production inhibitor izoniazid, but it did not reverse the decreased GABA level. As previously mentioned, benzodiazepines (diazepam, clonazepam) and barbiturates (phenobarbital) increase the affinity of the inhibitory neurotransmitter GABA for its recognition sites within the GABAA receptor complex and by directly influencing the chloride channel, which increases the influx of chloride anions into the neuron and causes subsequent hyperpolarization. Tiagabine and Vigabatrin, two new antiepileptic medications, appear to primarily exhibit their anticonvulsant effect through the GABA-ergic system. Felabate, gabapentin, and topiramate are other new antiepileptics linked to GABA-mediated inhibition that also share additional modes of action. Drugs like gabapentin, tigabine, and vigabatrin may be regarded as having developed in response to the so-called GABA theory of epilepsy. When administered to humans or animals, vigabatrin, an irreversible inhibitor of GABA transaminase, causes the level of synaptic GABA to increase by three times. Tiagabine prevents neuronal and glial GABA uptake, causing GABA synaptic events to be enhanced and prolonged as a result. Inhibitors of GABA absorption were demonstrated to have anticonvulsant properties in a number of experimental epilepsy models much earlier, but they were unable to pass the blood-brain barrier. This ruled out the possibility of using them as antiepileptic medications. Tiagabine and vigabatrin likely have mechanisms of action that are closely related to GABA-mediated events in the synaptic cleft, as was already mentioned, as opposed to some conventional and novel antiepileptic drugs that may block voltage-dependent sodium and calcium channels and hinder glutamate-induced excitation. For example, a number of antiepileptic medications, such as benzodiazepines (at high doses), carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, topiramate, and valproate, block sodium channels. Ethosuximide or zonisamide mainly affect T-type calcium channels, and felbamate, phenobarbital, and topiramate inhibit glutamate excitation [19]. Interestingly, gabapentin, a cyclic analogue of GABA, was designed as a GABA agonist easily passing the blood-brain barrier. However, no receptor activity of gabapentin was detected on the GABAA receptor complex, only increased GABA turnover being found in some rat brain regions . Also, gabapentin was documented to increase GABA level in brains of epileptic patients . It is evident now, that this antiepileptic drug binds to the specific unit of voltage- dependent calcium channel and inhibits intraneuronal calcium ion flux from the extraneuronal space . Two novel antiepileptic drugs, topiramate and felbamate, although possessing multiple mechanisms of action (see below), affect GABA-mediated inhibition as well. Specifically, the former seems to potentiate effects of endogenous GABA through a novel binding site on the GABAA receptor complex . The latter enhanced GABA-dependent chloride currents in rat hippocampal neurons . However, such effect in vitro was no longer evident in the absence of GABA and, moreover, felbamate was not shown to interact directly with the GABAA receptor complex**.**

Methods

Between July 2005 and December 2013, patients were chosen from the Pediatric Epilepsy Clinic at a referral medical college. 1108 children who were among 2200 kids referred for seizures had epilepsy, it was determined. Children (under the age of 18) with clearly defined epilepsy who had received treatment for a period of 2-3 years without seizures, after which their anti-epileptic medications (AED) were gradually discontinued over 2-3 months, were chosen, and who were followed up for at least 6 months. There were 148 of these kids identified, and risk factors and recurrence were also documented.

Profile Of Potential Antiepileptic Drugs Affecting Gaba-Mediated Inhibition

The primary mechanism of action of the neuroactive steroid ganaxolone is an increase in chloride channel permeability within the GABAA receptor complex. It is interesting that this neurosteroid binds to a steroid recognition site of the receptor complex. Despite having a moiety that is quite similar to progesterone, the medication has no hormonal effect. Maximal electroshock, pentylenetetrazol, bicuculline, and picrotoxin-induced convulsions were among the convulsive tests that showed ganaxolone to be effective in rodents. Despite having a definite antilethal activity against NMDA, it proved ineffective against strychnine- and NMDA-evoked seizures. Notably, ganaxolone's potency was even greater than that of diazepam and valproate in inhibiting pentylenetetrazol convulsions in fully kindled with pentylenetetrazol mice. Only ganaxolone showed antiepileptogenic activity because it could prevent kindling from forming; neither diazepam nor valproate had this effect. Additionally, the neurosteroid outperformed traditional antiepileptic medications in terms of adverse activity because mice's ambulatory behaviour was unaffected when given anticonvulsant doses within a certain range. The drug's potential effectiveness against myoclonic, tonic-clonic, and partial complex seizures is anticipated based on its preclinical characteristics. This may indicate that ganaxolone may share some more mechanisms of action. Indeed, it may also inhibit voltage-dependent calcium channels and reduce NMDA receptor-mediated events . However, like many GABA-enhancers, ganaxolone exacer-bated seizures in animal models of absence and at doses above 20 mg/kg it did produce synchronous spike and wave discharges . So far, very limited clinical data exist - ganaxolone proved effective against refractory infantile spasms (36 mg/kg/day) and complex partial seizures (1.5-1.8 g/day). Adverse effects were mainly associated with disturbed functions of the central nervous system – somnolence, asthenia, dizziness or stupor were occasionally observed .

Mechanisms of Action of Conventional and New Antiepileptic Drugs (AEDs).

AED	Enhancement of GABA-mediated excitation	Blockade of sodium channels	Blockade of calcium channels	Inhibition of glutamate-	Other
Benzodiazepines	+	+*			
Carbamazepine		+			
Ethosuximide			+ (T-type)		
Phenobarbital	+	+		+	
Phenytoin		+			
Valproate	+	+			+
Gabapentin			+ (L-type)		
Felbamate	+	+		+	
Lamotrigine		+	+ (L-type)		
Levetiracetam					+
Oxcarbazepine		+	+ (L-type)		
Tiagabine	+				
Topiramate	+	+	+ (L-type)	+	+
Vigabatrin	+				
Zonisamide		+	+ (T-type)	+	+

+, a documented mechanism of action (except for other mechanisms). Inconsistent data or data observed at supratherapeutic concentrations have not been included.

* This mechanism can work at high concentration of benzodiazepines, encountered at intensive treatment of status epilepticus.

Conclusions:-

The number of AEDs that are currently on the market has gradually expanded in recent years. This may make management decisions more difficult, but it also presents some welcome new options for efficiently individualising care. It has never been easier to customise pharmacological therapy to the unique characteristics of each patient because each AED is different from the others in terms of pharmacologic qualities, efficacy spectrum, side-effect profile, interaction potential, and cost. Even while first-generation medications are still the best option in the majority of cases, mounting data suggests that the initial use of newer medications for many illnesses may be entirely warranted. For instance, LTG may be an effective first-line therapy for the elderly due to its favourable tolerability profile, and it may be preferred to VPA in women with generalised epilepsy who are of reproductive age because of the potential dangers to the unborn child. In a patient with acute intermittent porphyria, GBP may be the most sensible treatment option for partial-onset seizures, while VGB is frequently the favoured option for infantile spasms brought on by tuberous sclerosis. The efficacy of various AEDs in treating comorbid diseases also affects treatment decisions.

We may anticipate a more judicious use of these drugs in the years to come thanks to the steady progress in our knowledge of the mechanisms of action, efficacy spectrum, and side effect profiles of AEDs in various patient groups and indications.

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