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REVIEW

Clinical response and tolerability of eslicarbazepine in treatment of partial onset seizures: impact of a novel metabolic pathway

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Abstract: Epilepsy is a common chronic neurological condition affecting 50 million people worldwide. Because at least 30% of patients with partial seizures do not achieve seizure control with the current antiepileptic drugs, there remains an urgent need for novel antiepileptic drugs with more favorable safety profiles. Eslicarbazepine acetate (formerly known as BIA 2-093) is a novel voltage-gated sodium channel blocker used as adjunctive therapy in the treatment of refractory partial-onset seizures. Eslicarbazepine acetate is a dibenzazepine that is chemically related to carbamazepine and oxcarbazepine, designed to avoid production of active metabolites, as occurs with both carbamazepine and oxcarbazepine. Carbamazepine is metabolized by the liver to the active metabolite, carbamazepine-10, 11-epoxide, which contributes to clinical toxicity. Eslicarbazepine acetate is reduced by esterases in the liver to the active metabolite eslicarbazepine, the S (+) enantiomer of licarbazepine,[27] without production of the 10,11-epoxide, resulting in a lower drug interaction potential and fewer adverse neurological effects. Further, while oxcarbazepine is a prodrug that is metabolized into both the S– and R– enantiomers of licarbazepine, eslicarbazepine acetate is metabolized to solely the S– enantiomer of licarbazepine. Eslicarbazepine acetate stabilizes the inactivated state of the voltage-gated sodium channels, preventing their return to an activated state and sustaining repetitive neuronal firing. Eslicarbazepine acetate also has a higher affinity for the inactivated state of the sodium channel compared with the resting state, suggesting enhanced selective inhibition of rapidly firing neurons associated with epileptic discharges. Consequently, eslicarbazepine acetate is less likely to bind to normally active neurons, and, therefore, less likely to cause adverse neurological effects. In clinical trials, eslicarbazepine acetate shows significant efficacy in reducing seizure frequency, and a favorable adverse effect profile at once per day doses of 800 mg or 1200 mg. This novel antiepileptic drug is a promising addition to the treatments for people with partial epilepsy.

Keywords: antiepileptic drugs, neurotransmission, seizures

Partial epilepsy and standard anticonvulsant agents

Epilepsy is a common neurological condition affecting 50 million people worldwide.[1] It is a chronic disorder in which seizures become recurrent and unprovoked. A seizure is a symptom that is caused by abnormal epileptic activity characterized by abnormal synchronization, excessive excitability and/or inadequate inhibition.[2] Repeated seizures may induce neuronal damage that could contribute to enhanced excitability and increased susceptibility to recurrent seizures,[3] leading to drug-resistant epilepsy. It has been estimated that up to 30% of patients with partial seizures do not achieve seizure control with current antiepileptic drugs.[4]

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Partial-onset seizure, which is the most common form of epilepsy, is characterized by abnormal epileptic activity arising from a localized region of the brain. Secondary generalization of partial seizures may occur when this abnormal activity spreads from the localized region to adjacent areas and then to the other brain hemisphere. This abnormal epileptic activity alters normal brain function, and its clinical manifestations depend on the region of the brain in which the abnormal activity takes place. Clinical symptoms of seizures are manifested as motor activity, sensory disturbances, cognitive impairment, or psychic phenomena, with or without alteration in consciousness or awareness.[2]

Significant growth in the drug armamentarium against partial epilepsy occurred in the twentieth century. Newer antiepileptic drugs with more favorable safety profiles than the standard antiepileptic drugs were developed in recent years. In the past, antiepileptic drug therapy for partial-onset epilepsy consisted of the first-generation antiepileptic drugs, including phenobarbital, phenytoin, carbamazepine, certain benzodiazepines, and valproic acid. Choosing an agent from this list may have seemed simple, but significant drug interactions and their side effect profile made their use complex. Adding to the complexity in the treatment of epilepsy has been the growth in the number of antiepileptic drugs used for the treatment of epilepsy seen in the recent years. The list of second-generation antiepileptic drugs available in the US at this time includes felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin, zonisamide. There are also newer third-generation antiepileptic drugs that include rufinamide, lacosamide, eslicarbazepine and retigabine, that may or may not be used in the US and other markets.

Contributing to this growing list of antiepileptic drugs is the interest in developing antiepileptic drugs with novel mechanisms of action and more favorable safety profiles. The discussion herein focuses on a new antiepileptic drug, eslicarbazepine acetate, presenting its mechanism of action, pharmacology, and novel metabolism which, in turn, impacts efficacy and tolerability in persons with epilepsy.

Pharmacology and mechanism of action of standard anticonvulsants

Antiepileptic drugs can shift cortical neurons from a state of increased excitability to a normal state by reducing excitation or enhancing inhibition. Antiepileptic drugs are able to regulate excitatory and inhibitory neurotransmission through their action on ion channels, neurotransmitter receptors, and neurotransmitter metabolism. The end result of their action is to suppress seizures and prevent the appearance of disruptive clinical manifestations. Furthermore, antiepileptic drugs aim to prevent increased neuronal excitability causing irreversible changes in neuronal structures that may lead to refractory or drug-resistant partial-onset seizures.

Inhibition of excitation

Sodium channel blockers

Antiepileptic drugs modify excitatory neurotransmission through their action on voltage-gated ion channels. Several antiepileptic drugs block sodium channels, including carbamazepine, felbamate, lamotrigine, oxcarbazepine, topiramate, valproic acid, and zonisamide. Phenytoin and carbamazepine are known to bind to and prolong the fast inactivation of voltage-gated sodium channels, causing pore occlusion by the cytoplasmic domains of the sodium channel. Phenobarbital and benzodiazepines may also inhibit the sodium channel at high concentrations when used at loading doses for the treatment of status epilepticus. Lastly, lacosamide enhances the slow inactivated state of the voltage-gated sodium channel that occurs under conditions of slightly prolonged depolarization and sustained neuronal firing activity, reducing the long-term availability of the voltage-gated sodium channels without enhancing fast inactivation.

Calcium channel blockers

Antiepileptic drugs may also regulate excitatory neurotransmission through their effect on calcium channels, although this is in general a secondary effect that is less characterized as a clinically important antiseizure mechanism. Gabapentin, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, topiramate, valproic acid, and zonisamide interact with voltage-gated calcium channels inhibiting calcium influx resulting in decreased depolarization.[5] At high concentrations, phenytoin inhibits axonal and nerve terminal calcium channels, and this effect may have clinical significance; phenytoin use has been reported to interfere with effective neuromuscular blockage by standard agents such as pancuronium.[6]

Inhibitors of presynaptic glutamate release

Antiepileptic drugs may alter glutamate neurotransmission presynaptically and postsynaptically, although the exact contribution of presynaptic neurotransmitter blockade by antiepileptic drugs to the overall balance of neuronal inhibition and excitation, in addition to the ion channel mechanism, is not clear.[7] Glutamate, an excitatory neurotransmitter released from presynaptic terminals, produces depolarization

by opening sodium or calcium channels. Carbamazepine, lamotrigine, phenytoin, and topiramate may block the presynaptic release of glutamate, but this is only part of several mechanisms by which these antiepileptic drugs produce their antiseizure effects.[7]

Glutamate receptor blockers

Antiepileptic drugs may modify excitatory neurotransmission through their action on glutamate receptors. Postsynaptically, glutamate binds to three ionotropic glutamate receptor subtypes, ie, NMDA, AMPA, and kainite, which may be regulated by certain antiepileptic drugs. Inhibition of NMDA by felbamate[8] and AMPA and kainite by topiramate[9] may result in reduced glutamate-mediated excitatory neurotransmission.

Stimulation of inhibition

Gamma aminobutyric acid (GABA) is an inhibitory neurotransmitter that produces opening of chloride or potassium channels, resulting in loss of excitability by allowing chloride ions into cells and potassium ions out of cells, respectively. Inhibitory neurotransmission is modified through effects on (GABA)A or (GABA)B receptors or GABA metabolism and reuptake. Despite their structural similarities to GABA, pregabalin and gabapentin may have a limited association with GABA neurotransmission or metabolism.[10,11]

Inhibitors of GABA reuptake

Tiagabine enhances the effect of endogenously released GABA by inhibiting GABA reuptake.[12]

Regulators of GABA metabolism

Vigabatrin causes irreversible inhibition of GABA transaminase, the first step in GABA deactivation, causing reduced catabolism of GABA and prolonged elevation of GABA levels. Valproic acid also increases levels of GABA by inhibition of GABA transaminase or through an increase in glutamic acid decarboxylase that is involved in GABA synthesis.[13]

GABA receptor agonists

Once released from presynaptic nerve terminals, GABA binds to both GABA A and GABA B receptors. The GABA A receptor forms a chloride-selective ion channel which causes fast inhibition. GABA B receptors are coupled to ligand-gated potassium channels via G proteins producing a longer duration of the hyperpolarization than the GABA A receptor.

Several antiepileptic drugs have been demonstrated to potentiate the effects of GABA on the GABA A receptor complex. Benzodiazepines enhance the binding of GABA to GABA A receptors, amplifying the influx of chloride into cells.[12] Topiramate potentiates GABA-mediated chloride entry into neurons.[14] Phenobarbital increases postsynaptic GABAergic inhibition by interacting with GABA A receptors. Zonisamide binds to the GABA-BZD receptor[12] complex and elevates levels of GABA. Levetiracetam may oppose the inhibiting action of zinc on GABA-gated currents. GABA B receptors may be regulated indirectly by increased[15] GABA levels made available by blockade of GABA reuptake by tiagabine or inhibition of GABA catabolism by valproic acid and vigabatrin.

Voltage-gated sodium channels and role in neuronal firing

The voltage-gated sodium channel is a complex of an α (260 kDa), β1 (36 kDa), and β2 (33 kDa) subunits.[16] The α subunit contains four homologous domains (I–IV), with each domain being composed of six transmembrane segments (S1–S6). The fourth segment (S4) is responsible for the voltage-dependent activation containing multiple positively charged arginine amino acids that are the gating charges. The loop between the fifth and sixth segments forms the channel pore, and the intracellular loop between the third and fourth domain forms the inactivation gate.[17]

The β1 and β2 subunits are auxiliary proteins with immunoglobulin-like folds[18] that modulate channel gating and cell-cell interaction.[17] It has been shown that coexpression of the β1 and β2 subunits accelerate channel gating to normal rates.[18–22] The β1 and β2 subunits are also structurally related to cell adhesion molecules, with immunoglobulin-like folds that allow binding to the extracellular proteins influencing neuronal migration, axonal extension, and interaction with other cells.[18,19,22]

During channel activation, there is movement of the S4 segment in response to membrane depolarization, causing a reduction in the forces holding the positive charges in an inward position.[23] Membrane depolarization causes movement of the positively charged amino acids to more outward positions, leading to a conformational change that opens the pore. After 1 millisecond, voltage-dependent fast inactivation of the channel occurs when the inactivation gate forming a hinged lid folds into the channel blocking the opening of the pore.[17] Hyperpolarization of the membrane then occurs, removing inactivation and returning the channel to the resting state. This allows the channel to be

activated again. A slow inactivated state may also occur when there is sustained depolarization, from which the channel recovers in seconds.[2,24]

The sodium channel is thus able to undergo voltage-dependent conformational changes that result in a closed resting state, an open state that conducts sodium ions, and a closed, nonconducting, inactivated state.[17,25] In the inactivated state, the channel cannot reopen as long as the membrane remains depolarized, whereas in the resting state, the channel is ready to open again if the membrane is depolarized.[25]

The sodium channel plays an important role in the generation of an action potential. The resting membrane potential of a neuron is around −70 mV but may vary in different nerve cells from −40 to −80 mV. An action potential is initiated when the neuronal membrane is depolarized beyond a threshold potential, and this threshold is lowest at the axon hillock where it is around −55 mV. When sodium enters the channel, the membrane depolarizes, bringing the membrane potential up above this threshold potential. There is then potassium and chloride channel opening, leading to efflux of potassium ions and influx of chloride ions, respectively, to repolarize and restore the membrane potential. This outward potassium and inward chloride current usually produces a negative after hyperpolarization that slowly returns to the resting level when the sodium channels shift from an inactivated to a resting state.[26]

The current associated with the action potential travels from the axon hillock down to the dendritic terminal where the depolarization causes the release of excitatory (glutamate) or inhibitory (GABA) neurotransmitters from the cells. The potentials generated are measured as excitatory or inhibitory postsynaptic potentials.[26]

Abnormally functioning neurons in an epileptic focus produce sustained excitatory postsynaptic potentials that have clusters of action potentials on the rising phase of the depolarizing wave and are followed by a period of after hyperpolarization. This abnormal activity is known as the paroxysmal depolarizing shift, and represents the spike-and-slow wave discharge seen on the electroencephalogram.[27–29]

Pharmacology of eslicarbazepine

Eslicarbazepine acetate (formerly known as BIA 2-093) is a novel voltage-gated sodium channel blocker[30] used as adjunctive therapy in the treatment of refractory partial-onset seizures. Eslicarbazepine acetate is a dibenzazepine that is chemically related to carbamazepine and oxcarbazepine. It was designed to avoid the production of toxic metabolites seen with the metabolism of carbamazepine.[31,32] The production of toxic metabolites is not seen with eslicarbazepine acetate due to a chemical variation at the 10, 11 position.[33] This chemical variation allows for differences in metabolism of both drugs.[34] Carbamazepine is metabolized by the liver to the toxic carbamazepine-10, 11-epoxide, while eslicarbazepine acetate is reduced by esterases in the liver to the active metabolite, eslicarbazepine, the S (+) enantiomer of licarbazepine,[35] allowing for a lower drug interaction potential and for fewer adverse neurological effects.[32,36] Furthermore, eslicarbazepine acetate was designed to overcome enantiomeric impurity and unnecessary production of enantiomers or diastereoisomers of metabolites and conjugates, without losing pharmacological activity.[31,32] Oxcarbazepine is a prodrug that is metabolized into both the S– and R– enantiomers of licarbazepine while eslicarbazepine acetate is metabolized to the S– enantiomer of licarbazepine.[34] This conversion of eslicarbazepine acetate to S-licarbazepine is believed to be the reason for fewer adverse neurological effects being seen in rats than for oxcarbazepine.[31]

Eslicarbazepine

Eslicarbazepine acetate and its major metabolite, eslicarbazepine, stabilize the inactivated state of the voltage-gated sodium channels, preventing their return to an activated state and sustaining repetitive neuronal firing.[37] Eslicarbazepine acetate has a higher affinity for the inactivated state of the sodium channel compared with the resting state, suggesting an enhanced selective inhibition for rapidly firing neurons, such as those producing the paroxysmal depolarizing shift over those displaying normal activity.[33] The affinity of eslicarbazepine acetate for the inactivated state is similar to that of carbamazepine, but its affinity for the resting state is three times less.[32,34] Consequently, eslicarbazepine is less likely to bind to normally active neurons, and, therefore, less likely to cause adverse neurological effects.[38] Eslicarbazepine acetate does not appear to interact with the receptors for benzodiazepine, GABA, or glutamate.[30,39–41] Eslicarbazepine acetate does not affect calcium channels coupled to the presynaptic release of glutamate.[40]

Rationale for combination with carbamazepine

The efficacy and tolerability of once-daily eslicarbazepine acetate when used as add-on therapy in adults with refractory partial-onset epilepsy has been investigated in several multicenter, randomized, double-blind, placebo-controlled studies. In one Phase II study, once-a-day dosing was found to be as effective as when the same daily dose was given twice a day.[42]

Daily doses given as one or two equally divided doses from 400 to 1200 mg were administered and tested against placebo, showing that once-a-day dosing allowed for higher peak plasma concentration of the active metabolite. In addition, this study showed a favorable safety profile, and hyponatremia was only seen in one patient (1.0%). The study also showed that eslicarbazepine acetate was effective as add-on therapy in patients with partial-onset epilepsy resistant to treatment with one or two standard antiepileptic drugs. In a Phase III study, eslicarbazepine acetate, given as 800 mg and 1200 mg once a day, was well tolerated and more effective than placebo in patients with refractory partial seizures with at least four partial-onset seizures per four weeks despite treatment with one or two antiepileptic drugs.[43] The seizure frequency was significantly lower with once daily dosing of eslicarbazepine acetate given at 800 mg and 1200 mg than with placebo or 400 mg of eslicarbazepine acetate. More patients became seizure-free at these doses during the titration and maintenance periods. There was a very low incidence of psychiatric events, which consisted of depression, anxiety, insomnia, and irritability, and there were no reports of suicide. There was also a low incidence of rash. Laboratory studies revealed no increased risk of hyponatremia, abnormal lipid profile, or glucose abnormalities. The most common adverse events were dizziness, headache, and somnolence, and higher doses of eslicarbazepine acetate were associated with an increased incidence of adverse events. Dizziness, somnolence, diplopia, and nausea were the most common adverse events causing discontinuation of medication. Carbamazepine was the most frequently used concomitant antiepileptic drug (56%–62% of patients), followed by lamotrigine (25%–27%), and valproic acid (22%–28%), and eslicarbazepine acetate did not produce any significant changes in plasma concentrations of the concomitant antiepileptic drugs. The coadministration of carbamazepine and eslicarbazepine acetate, two sodium channel blockers, may help produce a stronger synergistic response. This study showed a 30% and 46% median reduction of seizures during the maintenance period in patients using both carbamazepine and eslicarbazepine acetate at doses of 800 mg and 1200 mg a day, respectively.

A one-year, open-label extension study showed a sustained reduction in seizure frequency from baseline when using 800 mg or 1200 mg a day.[44] A significant long-term improvement was seen in seizure worry, social function, energy and fatigue, and cognitive function, as assessed by the seven-scale Quality-of-Life in Epilepsy Inventory-31.[45] Additionally, depressive symptoms were significantly reduced with long-term use of eslicarbazepine acetate as assessed by the 10-item Montgomery-Asberg Depression Rating Scale.[46]

Conclusion

Several aspects of eslicarbazepine acetate draw attention to developing antiepileptic drugs with a simple titration schedule and once-daily dosing, good tolerability, and proved effectiveness in the reduction of partial-onset seizures. These characteristics of eslicarbazepine acetate allow for increased drug compliance in patients with epilepsy. Identifying other means to improve drug compliance should be put into future practice when developing new antiepileptic drugs. Other areas that are becoming important in the future care of patients with epilepsy include identifying channel mutations or altered channel structures leading to drug resistance, creating antiepileptic drugs that specifically target those mutated channels, and developing neuroprotective drugs with antiepileptogenic properties that could attenuate the progression of epilepsy leading to drug resistance by interfering with the processes that promote permanent neuronal excitability, abnormal synaptic reorganization, or neuronal loss which are highly prone to generating seizures.

Disclosure

The authors report no conflicts of interest in this work.

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