

SEIZURE INDUCED BY ANTIEPILEPTIC DRUGS

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The purpose of any antiepileptic drug is to suppress seizure activity in epileptic patients, but certainly not to aggravate it. Positive evidence indicates that antiepileptic drugs may worsen a pre-existing seizure by increasing its frequency or inducing a new type of seizure. In this review we assess the true extent of this problem, and the types of seizures induced by the currently available antiepileptic drugs.

The Extent of the Problem

Reaching a conclusion that a particular antiepileptic drug has the potential to worsen certain types of seizures may be determined by several factors.¹ Some of these factors include the tendency for some types of seizures, especially those in children, to fluctuate in their severity.² This fluctuation may be spontaneous, with no obvious reasons. Based on this, it would be difficult to decide if the fluctuation was related to the antiepileptic drug used or to the pathogenesis of that type of epilepsy. The other important factor to be excluded before naming an antiepileptic drug as a pro-epileptic agent is if this event of aggravation was only a coincidence and not related to inappropriate control of the seizure. The inability to control the seizure may result from administration of small doses of antiepileptic drug, or from giving the wrong drug for a certain type of seizure. Unfortunately, clinical trials performed on a drug that has antiepileptic activity are only designed to detect if that particular drug is efficient in suppressing seizure activity but cannot detect potential worsening of the seizure. Furthermore, it is known that polytherapy with antiepileptic drugs is necessary to control certain types of seizures in some patients. The polytherapy strategy increases the possibility of drug-drug interaction manifested by an increase in the level of the active free drug, thus aggravating the seizure. Based on this, attributing a pro-epileptic effect to an antiepileptic drug should be done cautiously. This may be possible if: 1) the aggravation of seizure occurs at therapeutic doses, and with normal serum drug level below the toxic range, because at high doses, different mechanisms may operate, and, 2) if the aggravated seizure subsides after suspension of the drug and again gets worse after its reintroduction.

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Seizures Induced by Current Antiepileptic Drugs

The types of seizures induced or aggravated by antiepileptic drugs are summarized in Table 1.

Phenobarbital (PB)

This drug mediates its antiepileptic action by potentiating gamma-aminobutyric acid (GABA) inhibition by binding to a specific site on the GABA_A receptor chloride channel complex.³ PB was reported to induce negative myoclonus with unilateral central spike-and-wave in electroencephalogram (EEG) in a child with atypical benign rolandic epilepsy.⁴ PB was also reported to induce tonic seizures in children with Lennox-Gastaut syndrome,⁵ and aggravated absence seizures in children.¹

Benzodiazepines (BZDs)

These drugs induce their antiepileptic effect by a mechanism similar to PB, but by binding to a different site on the GABA_A receptor chloride channel complex.³ Tonic seizures in patients with Lennox-Gastaut syndrome were exacerbated after using iv diazepam and nitrazepam. The worsening of the seizure was associated with diffuse rhythmic spikes in EEG. Moreover, clonazepam induced tonic-like seizures in infants with West syndrome.¹

Phenytoin (PHT)

This drug acts by the use- and voltage-dependent block of sodium channels.³ It has the highest number of reports of paradoxical action. This may be related to its popularity at the time when these events were being reported, and to its nonlinear pharmacokinetic effect. The drug increased the bursting frequency and changed the pattern of seizure from tonic-clonic to a seizure with opisthotonic posture.⁶ The

TABLE 1. Summary of the type of seizures induced or aggravated by antiepileptic drugs.

Antiepileptic drug	Type of seizure
Phenobarbital	Negative myoclonus, tonic and absence
Benzodiazepines	Tonic-clonic
Phenytoin	Different types (see text)
Carbamazepine	Tonic, atonic, absence, myoclonic
Oxcarbazepine	Absence and myoclonic
Valproate	Myoclonic and status epilepticus
Ethosuximide	Generalized nonconvulsive and atonic

Lamotrigine	Myoclonic
Gabapentin	Absence and myoclonic
Vigabatrin	Myoclonic

drug also induced central nervous system toxicities such as choreoathetosis and brainstem-cerebellar signs, a phenomenon later referred to as hydantoin encephalopathy.⁷ However, all these effects were produced at high doses of the drug. Not only did PHT enhance seizures in human, but also did so in experimental animals. The drug enhanced seizures induced by pentylenetetrazol, quisqualate and penicillin.⁸ Additionally, it increased the severity of amygdaloid-kindled seizures and produced brain damage secondary to this effect.⁹

Carbamazepine (CBZ)

The mechanism of action of carbamazepine is similar to that of PHT.³ CBZ is reported to exacerbate different types of seizures. It can aggravate generalized seizures such as tonic, atonic, atypical and typical absences and myoclonic seizures.¹⁰ The drug exacerbated seizure frequency in patients with Angelman's¹¹ and Landau-Kleffner syndromes.¹² Additionally, it was reported that the drug could aggravate tonic-clonic seizures including status epilepticus. This aggravation was accompanied by EEG changes such as the appearance of generalized spike-and-wave activity.¹³

Oxcarbazepine (OXC)

This agent is a 10-keto analogue of CBZ, and has a similar mechanism of action.³ It is reported that it may worsen absence and myoclonic seizures.

Valproate (VPA)

The mechanism of the antiepileptic activity of this drug is not clear. However, it is believed that VPA inhibits sodium channels or potentiates GABA inhibition in the central nervous system.³ This drug induced myoclonic seizure without signs of encephalopathy in a five-year-old mentally retarded child, and was abolished by reducing the dose of VPA.¹⁴ In epileptic patients, high doses of VPA induced status epilepticus¹⁵ and increased spike-wave frequency in EEG.¹⁶ VPA produced a state of encephalopathy characterized by a worsening of seizure as well as cognitive impairment. The mechanism of this phenomenon is not well understood but may be related to hyperammonemia induced by toxic doses of the drug.¹⁶

Ethosuximide (ESM)

This drug induces its antiepileptic action by reducing the low threshold, voltage-dependent calcium conductance in thalamic neurons.³ It aggravated generalized nonconvulsive seizures,¹⁷ and was also reported to worsen atonic seizures in patients with myoclonic juvenile epilepsy.¹⁸ The drug exacerbated tonic-clonic seizures in children with absence epilepsy.¹⁹ In experimental animals, ESM at high concentrations paradoxically increased the

spontaneous bursting induced by penicillin,²⁰ and lowered the threshold for seizure produced by pilocarpine.⁹ The drug enhanced seizure susceptibility in rats by increasing the level of glutamate in the cortex and the brain stem.²¹ Moreover, ESM increased the susceptibility of mice to seizures induced by NMDA agonists,⁸ and enhanced the epileptic activity induced by picrotoxin in cultured cortical neurons.²²

Lamotrigine (LAG)

The mechanism of action of this drug as an antiepileptic agent is by reducing glutamate release secondary to inhibition of voltage-dependent sodium channels.³ This drug aggravated myoclonic seizures when used as an add-on treatment. The worsening of the seizure was evident after three months of starting the therapy, and was associated with worsening of the interictal EEG changes.⁴

Gabapentin (GBP)

This drug is a GABA analogue. It produces its antiepileptic effect by binding to specific high-affinity binding sites in the brain. These sites have not been identified functionally. This drug exacerbated absence and myoclonic seizures in a 14-year-old boy with Lennox-Gastaut syndrome.²³ The drug was also reported to induce myoclonus in patients with partial epilepsy.²⁴

Vigabatrin (VGB)

This drug increases GABA levels by irreversible inhibition of GABA-aminotransferase. It may worsen myoclonic seizures.²⁵

The phenomenon of seizures induced by antiseizure drugs is complex. It is obvious from the review that certain antiepileptic drugs can either aggravate already existing seizures or induce them. This paradoxical reaction may be dose-related, idiosyncratic or a result of overdose. Additionally, using inappropriate drugs for a particular type of epilepsy may worsen seizure. The choice of antiepileptic drug by clinicians should be based on precise diagnosis. The pharmacological explanation of seizure induced by antiseizure drugs is not completely understood.

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