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Review Article

Impact of anti-epileptic drugs on cognition: a review

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ABSTRACT

Epilepsy is a chronic disorder of brain caused by various factors which may vary according to the patient age. In epilepsy threshold for seizure generation get reduced. It may affect patient's living and increases morbidity. Anti-epileptic drugs are given as mono or poly-therapy for seizure control. These anti-epileptics produce side-effects which are dose and duration of the treatment dependent. One of the important side effects is impact on cognitive function of the patient. However, some anti-epileptic medications also cause improvement in the cognitive function. Newer anti-epileptics are providing better compliance and impact as compared to older ones.

This review article provides details of impact of anti-epileptic drugs on cognitive functioning.

Keywords: Epilepsy, Seizure, Epileptogenesis, Partial seizures, Generalized seizures, Cognition, Anticonvulsants, Anti-epileptics

INTRODUCTION

Epilepsy is a neurological disorder characterized by epileptic seizures. The word "epilepsy" has its origin in ancient Greece which means "to seize, possess, or afflict". Epilepsy is an umbrella term which refers to a clinical phenomenon rather than a single disease entity and is characterized by unpredictable seizures.

It is a chronic non-communicable disorder of brain.[1] It is one of the most common neurological disorders that affects people of all ages.[2]

Incidence of epilepsy ranges from 30 to 57 per 100,000 population.[3] These rates vary with age, being highest in infants and young children, and then decreasing throughout adulthood until approximately 60 years of age, when they again begin to increase. The overall prevalence of epilepsy is approximately 6 per 1000 population.[3]

The mainstay treatment of epileptic seizures is anticonvulsant medications. These antiepileptic drugs when used for long-term, may also affect cognitive functions of the patient. This review article focuses on the effects of common anti-epileptic drugs on the cognitive functions of the patients of epilepsy.

Etiopathology

Causes of epilepsy vary according to the age group. Many without a clear cause may have genetic correlation. Brain malformations, lack of oxygen during birth, inter-cranial hemorrhage, acute CNS infections, fever,

infections, brain tumor (rarely), idiopathic causes, congenital conditions (Down's syndrome; Angelman's syndrome; tuberous sclerosis and neurofibromatosis), illicit drug use and various drugs like alkylating agents, anti-malarials, antimicrobials, anaesthetics, analgesics, immuno-modulatory drugs, lithium are some important etiological factors.[4]

During an epileptic seizure, neuronal network transforms into a hyper excitable state.[4] From initial CNS injury to the occurrence of the first seizure there may be a delay of months to years. The injury lowers the seizure threshold in the affected region. In many genetic and idiopathic forms of epilepsy, epileptogenesis is presumably determined by developmentally regulated events.Pathological findings of the hippocampus from patients with temporal lobe epilepsy suggest that some forms of epileptic seizures are related to structural changes in neuronal networks.[4]

Diagnosis

According to the International League Against Epilepsy (ILAE), epilepsy is defined by any of the following conditions:[5]

- At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart.
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
- Diagnosis of an epilepsy syndrome.

Epilepsy includes many diseases and syndromes.[3,4] Table 1 gives classification of various epileptic syndromes.

Epilepsy can be idiopathic when the disorder is not associated with other neurologic abnormalities. Symptomatic indicates that such an abnormality is present and the cause is known. Cryptogenic refers to syndromes that are presumed to be symptomatic but the cause in a specific patient is unknown.[1,4]

Furthermore, epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past that age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.[6]

EEG findings of an established seizure is a typical electrographic "spike" due to intense firing of a large number of local excitatory neurons, causing an apparent hyper-synchronization of the excitatory bursts across a relatively large cortical region.[4] A relatively long-lasting depolarization of the neuronal membrane caused by influx of extracellular calcium (Ca^{++}) results in bursting activity in individual neurons, which causes opening of voltage-dependent sodium (Na^{+}) channels, influx of Na^{+} and generation of repetitive action potentials. This causes generation of hyper-polarizing after potential mediated by γ-amino butyric acid (GABA) receptors or potassium (K^{+}) channels, depending on the cell type. The synchronized bursts from a sufficient number of neurons result in a so-called spike discharge on the EEG.[4]

Management of epileptic seizures

Antiepileptic drugs act primarily by blocking the initiation or spread of seizures.[4] Various mechanisms include inhibition of Na^{+}-dependent channels , inhibition of voltage-gated Ca^{++} channels, facilitating the opening of potassium channels, attenuating glutamate activity, potentiating GABA receptor function, increase in the availability of GABA and modulation of release of synaptic vesicles contents.[4]

Table 2 gives an account of various first and second line antiepileptic drugs used in different forms of epileptic seizures. There is currently no drug known to prevent the formation of a seizure focus following CNS injury.[4]

These drugs have a significant impact on cognitive function of the patient which can either improve or deteriorate the cognition. The impact of anti-epileptic drugs are mainly due to the dose and frequency, patient compliance and susceptibility, past psychiatric history and poly-therapy.[7,8]

Phenobarbital and primidone

Phenobarbitone was the first efficacious as well as cheapest and least toxic antiepileptic drug. Phenobarbital and primidone both are now days being used as a second line drugs in generlized tonic-clonic seizure as well as in partial seizure. In patients of convulsive disorder on phenobarbital no severe adverse impact was seen on cognition although a little reduction in attention was observed however, some studies have shown adverse cognitive effects with the use of phenobarbital.[6,9] More adverse effects on motor performance and attention has been found with primidone.[10] Usual adult daily dose of phenobarbital is 90-180 mg and target range of plasma concentration is 10-40 µg/ml and for primidone daily adult dose is 750-1250 mg and target plasma concentration is 5-12 µg/ml.[3]

Phenytoin

Phenytoin is a barbiturate analogue. It is first choice drug in generalised tonic-clonic seizure and simple and complex partial seizure. It is also used in trigeminal neuralgia. Concentration, memory, visuomotor functions, mental speed show decline with use of phenytoin.[11] Some study show no effect on cognition whereas some show decline in cognitive function which is dose related.[7,12] Long term administration of phenytoin does not produce significant adverse effects on cognitive functions except some visually guided motor functions.[11] Usual adult daily

dose of phenytoin is 300-500 mg and target range of plasma concentration is 5-25 µg/ml.[3]

Carbamazepine

It was introduced mainly for trigeminal neuralgia but now a day it has become first line anti-epileptic drug. It is still the drug of choice for all types of neuralgia. Information processing and attention have shown decline with use of carbamazepine.[13,16] Poorer verbal fluency in adults, decline in memory and arithmetic performance has been noted after withdrawal of carbamazepine. Effect on cognitive profile is worse with carbamazepine as compared to levetiracetam but as compared to phenytoin impact is better on cognitive functions.[17,18]

Carbamazepine treated patients of benign rolandic epilepsy had shown improvement in story recall.[20] Longer duration of intake, poly-therapy and higher doses are believed to be the main causative factors having impact on cognitive function.[15,20,21] Usual adult daily dose of carbamazepine is 600-1800 mg and target range of plasma concentration is 4-12 µg/ml.[3]

Sodium valproate and ethosuximide

Sodium valproate is a branched chain aliphatic carboxylic acid having broad spectrum anticonvulsant action. It is first choice drug in absence, myoclonic and atonic seizures whereas it is second line drug in generalized tonic-clonic seizures. It does not cause much alteration in cognitive impairment.[22-24] Some studies show mild impairment in adult, elderly patients and child.[25-27] However, according to a recent study attentional dysfunction was more commonly seen with valproic acid than ethosuximide.[28]

Ethosuximide is effective only in absence seizure. Improvement in cognitive function has been seen with the use of ethosuximide.[29] Usual adult daily dose of sodium valproate is 1000-3000 mg and target range of plasma concentration is 50-150 µg/ml and for ethosuximide usual adult daily dose is 500-1000 and target range of plasma concentration is 40-100 µg/ml.[3]

Tiagabine

Tiagabine is a newer antiepileptic drug given only as add on therapy in patients of partial seizures. Cognitive functions had not been affected with tiagabine use.[14,30,31] Improvement in motor speed, concentration and verbal fluency has been reported with the use of tiagabine.[32] Usual adult daily dose of tiagabine is 32-56 mg and target range of plasma concentration is 5-70 µg/ml.[3]

Vigabatrin

Vigabatrin is a newer antiepileptic drug effective in refractory epilepsy and approved only as adjuvant medication. Cognitive functions remain unaffected and memory retrieval improved significantly with vigabatrin use.[33] Episodic memory, semantic memory and mental processing showed improvement.[34] Visual field restriction is the only limitation seen with vigabatrin use.[35] Vigabatrin given at 2 gm/day has no adverse effect on cognition except reduction in response time in central cognitive processing ability.[36] Usual adult daily dose of vigabatrin is 1000 mg.[3]

Clobazam

It is a benzodiazepine introduced as anxiolytic but later found effective in partial, atonic seizures. Improvement in alertness and attention has been reported in children with the use of clobazam.[37] In rolandic epilepsy paediatric age group patients tolerated well.[38] Usual adult daily dose of clobazam is 20-40 mg.[3]

Zonisamide

It is a newer antiepileptic having weak carbonic anhydrase activity. Memory and attention problems and long lasting impact on cognitive function has been reported in patients taking zonisamide.[39] Impaired cognitive function is the most common reason of discontinuation.[40] Dose related decline in attention, memory and verbal fluency has been noted.[41] Usual adult daily dose of zonisamide is 200-600 mg and target range of plasma concentration is 10-40 µg/ml.[3]

Gabapentin

Gabapentin is a lipophilic GABA derivative mainly used as second line drug for complex partial seizure. It is also given as add-on drug with first line anti-epileptics for reducing seizure frequency in refractory partial seizures. Use of this drug has shown no or little impact on cognition rather it has shown improvement in cognition.[42] Usual adult daily dose of gabapentin is 1200-2400 mg and target range of plasma concentration is 4-16 µg/ml.[3]

Pregabalin

Pregabalin is newer congener of gabapantin being used for neuropathic pain and other types of chronic pain. Cognitive impairment has been reported in some studies.[43] Verbal and visual memory has been affected and abnormal thinking has been reported with the use of pregabalin.[44,45] Usual adult daily dose of pregabalin is 150-600 mg.[3]

Topiramate

Topiramate has weak carbonic anhydrase activity with broad anticonvulsant spectrum. It can be used as mono-therapy as well as supplementing first line antiepileptic medications. Cognitive adverse events are very common in children with use of topiramate.[46] Adverse events are the most important factor for topiramate withdrawal.[47] After withdrawal verbal fluency, attention and verbal and

spatial span was improved.[48] Patients suffering from temporal lobe epilepsy and having past psychiatric problems are more vulnerable to cognitive impairment with topiramate.[8,49] Usual adult daily dose of topiramate is 200-400 mg and target range of plasma concentration is 2-25 µg/ml.[3]

Lamotrignine

Lamotrigine is a newer anticonvulsant having similar profile as carbamzepine. It is used initially as add-on drug but now found effective as mono-therapy as well. No adverse effect has been reported with lamotrignine use rather improvement has been seen in attention, short-term memory and motor functions.[50-52] Usual adult daily dose of lamotrigine is 100-250 mg and target range of plasma concentration is 2-20 µg/ml.[3]

Oxcarbazepine

A newer congener of carbamazepine but have less side effect profile and indicated as first line drug for generalised tonic-clonic seizures. No or less cognitive impairment is seen with patients treated with oxcarbazepine mono-therapy.[53,54] One study shows better information processing in patients on oxcarbazepine.[55] Usual adult daily dose of oxcarbazepine is 1200-2400 mg and target range of plasma concentration is 5-50 µg/ml.[11]

Levetiracetam

Levetiracetam a unique anticonvulsant drug on which none of the major anticonvulsant mechanisms appear to be applicable. It is being used mainly as add-on therapy for generalized and partial seizure. No cognitive adverse effects were reported with use of levetiracetam.[56,57] It increases memory and reaction time. An open study reported improved cognition in patients of atypical benign childhood epilepsy.[58] In patients with impaired cognition, levetiracetam can be substituted for improving cognition.[57] Usual adult daily dose of levetiracetam is 1000-3000 mg and target range of plasma concentration is 20-60 µg/ml.[3]

As compared to older anti-epileptic drugs the newer anti-epileptic drugs have less detrimental impact on cognition profile of the patient. Among older anti-epileptic drugs ethosuximide maintained best cognitive profile whereas in newer anti-epileptic group levetiracetam reported least interference with cognition of the patient receiving it.

CONCLUSION

Effect on cognition for some anti-epileptic drugs have been explored completely but many other are still to be explored. Some studies fail to indicate type of epilepsy or focal point of epileptic seizures. Cognitive functions are also not well defined and the methodology also needs to be systemic to fulfil the loopholes and improve the effectiveness and accuracy of the study.

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