REVIEW

PHARMACOTHERAPY OF ANTIEPILEPTICS IN PEDIATRIC PATIENTS WITH EPILEPSY - A REVIEW

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Submitted on: 20.12.17; Revised on: 10.01.18; Accepted on: 20.01.18

ABSRTACT

Epilepsy is more common in children than in any other age group apart from the geriatric population. Indeed epileptic seizures are more likely to occur on the first day of life than at any other time. The impact of epilepsy on every aspect of both the lives of the child and family is significant. Issues such as mental retardation, subtle neuropsychologic disturbances, cognitive problems, behavioral problems and learning difficulties are major factors affecting the children with epilepsy. The rate of new-onset seizures and epilepsy thereafter falls steeply but remains high throughout infancy, dropping further during childhood and into adolescence. Drug treatment forms one of the most important forms of therapy for a vast majority of epilepsy patients. The majority of patients can achieve complete seizure control by taking antiepileptic drugs (AEDs). AEDs can effectively control seizures in 70-80% of children with epilepsy. Antiepileptic drugs can be effective, but like all drugs acting on the CNS, cause side effects. AEDs do not 'cure' epilepsy; there is no evidence that they can influence the prognosis of the epilepsy. The decision to prescribe AEDs should be shared with the patient, who should be provided with information about the drug (including indications, side effects and licence status) and information about the condition including risks of not taking medication.

KEYWORDS: Epilepsy, Seizures, Antiepileptic drugs (AEDs)

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Indian Research Journal of Pharmacy and Science; 15(2017)1216-1223;
Journal Home Page: https://www.irjps.in
DOI: 10.21276/irjps.2017.4.4.8

INTRODUCTION

An epileptic seizure is a clinically discernible event, which results from the synchronous and excessive discharge of a group of neurons in the cerebral cortex. The manifestation of a seizure depends on where in the brain it starts and how far and fast it spreads. Epileptic seizures usually have a sudden onset, spread in a matter of seconds or minutes and, in most instances, are brief. The seizure can be divided into a prodrome (the occasional recognition that a seizure will occur, sometime hours or daysbeforehand), the seizure, which may include an aura (symptoms present at the beginning of a seizure), and lastly the post-ictal state (a period after the seizure during which the patient is usually confused). The mechanisms underlying seizure initiation and spread are still poorly understood, but involve the aberrant synchronisation of excitatory neurons, abnormal neuronal firing (e.g. burst firing) and a failure of inhibition. [1]

Around 4%–10% of children suffer at least one seizure in the first 16 years of life. [2] The incidence is highest in children below 3 years of age, with a decreasing frequency in older children. [3] Epidemiological studies reveal that approximately 150,000 children will sustain a

first-time unprovoked seizure every year, and of those, 30,000 will develop epilepsy. [2]

Classification: Seizures can be clinical or subclinical (electrographic) with EEG but no clinical manifestations. The International League against Epilepsy (ILAE) classification system is summarized in **Table no.1** [4]

I. Seizure classification
1. Partial (focal) seizures
A. Simple (normal consciousness)
B. Complex (disturbed level of consciousness)
C. Simple evolving to complex partial
2. Generalized
A. Primary generalized (generalized from the onset)
B. Secondary generalized (starting as simple or complex partial)
3. Unclassified
II. Classification of epilepsy syndromes
1. Localization related (focal)
A. Idiopathic (benign rolandic epilepsy)
B. Cryptogenic (non-lesional partial epilepsy)
C. Symptomatic (mesial temporal sclerosis, glioma)
2. Generalized
A. Idiopathic (Absence epilepsy)
B. Cryptogenic (Myoclonic astatic epilepsy)
C. Symptomatic (Infantile spasms, Lennox Gastaut syndrome)
3. Undetermined (severe myoclonic epilepsy of infancy)
4. Special (situation related such as febrile seizures)

Table no.1 - International classification of seizures and epilepsy syndromes.

A partial (focal) seizure can be simple with normal consciousness or complex when consciousness is impaired (not necessarily completely lost). Patients may become confused disoriented or have no memory of a complex partial seizure, however, they always remember a simple attack (aura). Therefore, an aura is a simple partial seizure with clinical manifestations that depends on the involved region of the brain. Partial seizures can be motor (frontal), sensory (parietal), visual (occipital), autonomic or psychic (temporal). An initial simple partial seizure may spread to neighboring or remote brain regions resulting in impaired consciousness (simple to complex) or in a generalized tonic-clonic seizure. This later type is called a secondarily generalized seizure, to differentiate it from seizures that are generalized from the onset (primary generalized). Myoclonic, atonic, and absence seizures are all primary generalized seizures. Note that the majority of generalized tonic clonic seizures in children are secondarily generalized, which has important diagnostic and therapeutic implications. Epilepsy syndromes are associated with one or more seizure types and other characteristic clinical, EEG, or prognostic characteristics. For example, febrile seizures are a common special (situation related) benign epilepsy syndrome characterized by focal (atypical) or generalized (typical) seizures. [5]

ETIOLOGY

Epilepsy is a symptom of an underlying brain disorder. It can present many years after a brain insult (such as perinatal hypoxia, brain injury etc). Indeed, it is not uncommon for people with a brain injury in childhood to present with epilepsy in their twenties. This is termed remote symptomatic epilepsy.

In Approximately 40–50% of cases, although suspected, no known cause is found. With the advent of more advanced neuroimaging, this number is dwindling. The range of causation varies with age, and geographical location. The commonest acquired causes in young infants are perinatal hypoxia/asphyxia, perinatal intracranial trauma, metabolic disturbances, congenital malformations of the brain, and infection. In young children and adolescents, idiopathic (genetically determined) epilepsies account for the majority of seizure disorders.

Adult epilepsies can result from initial causation in childhood but, in young adults, alcohol and head injury are amongst the commonest causes. In older adults, brain tumours are responsible for epilepsy in one-third of patients between the ages of 30 and 50 years, and cerebrovascular disease is the commonest cause of those over 50 years. In developing countries, parasitic disorders such as cysticercosis and malaria are important causes. [1]

PHARMACOTHERAPY

Children with seizure disorders require prolonged antiepileptic drug (AED) therapy for atleast two seizure-free years. Initial treatment approaches focus on drug therapy, either monotherapy or adjunctive therapy. Treating children with epilepsy differs from treating adults because cognitive effects of AEDs may be more serious than occasional seizures. Another concern is that biological half-life of AEDs in children varies significantly from that of the adults, because these medications are eliminated faster in children, so, doses generally have to be adjusted. This is especially true for drugs that are metabolized by the liver Seizure medication are available in two types: narrow and broad spectrum AEDs. Some patients may need more than one medication to prevent the epileptic seizures more effectively. [6-8]

Carbamazepine (CBZ):

Carbamazepine is a major first-line anti-epileptic drug. It causes frequency dependent blockade of sodium channels and induces its own metabolism. It is the drug of choice for complex partial and secondary generalized seizures in both adults as well as children. Its use is more controversial in generalized epileptic syndromes of childhood. It can worsen atypical absence, tonic, myoclonic seizures. In children with Lennox-Gastaut syndrome, it can exacerbate certain seizures such as myoclonic and drop attacks. [9] The initial maintenance dose is 5 to 10 mg/kg/day. It can be increased by 5-10 mg/kg/day at weekly intervals and the final doses of 30 mg/kg/day are not unusual in children. It is one of the safest anti-epileptic drugs for use during pregnancy. There is a good correlation between the dose of carbamazepine and its blood levels. Therefore, regular therapeutic drug monitoring is very useful. The common side effects are allergic rash, leucopenia, ataxia, dizziness, diplopia and vomiting. Hyponatremia may develop but this does not require routine monitoring. Elevated enzymes are found in up to 5-10% of patients. Slow titration over 1-2 weeks will reduce the side effects and will have better tolerance. [10]

The United States (US) Food and Drug Administration (FDA) approved CBZ in 1968 as first-line and adjunctive therapy for treatment of focal seizures (FS) and generalized tonic–clonic seizures (GTCS). No differences in efficacy were observed between CBZ and PHT as first-line treatment in children with FS and GTCS. [11, 12]

Phenytoin (PHT)

Phenytoin sodium is one of the most commonly used AEDs in the world since 1953. It blocks the ionic movements in sodium channel, suppresses the buildup of paroxysmal electrical activity, blocks post-tetanic potentiation and thus prevents the spread of seizures. It also has an inhibiting effect on calcium and sequestration of calcium ions in nerve terminal inhibits voltage-dependent neurotransmitters release at the synapse. Phenytoin is one of the most commonly used first-line or adjunctive treatments for partial and generalized seizures, Lennox-Gastaut syndrome, status epilepticus and childhood epileptic syndromes. It is not indicated for myoclonus and absence seizures. Phenytoin is a useful drug during neonatal period. Usually, it is administered after phenobarbital has failed. [13] The initial intravenous loading dose in neonates is 15-20 mg/kg. When neonates with seizures were randomly assigned to receive either phenobarbitone or phenytoin, both were equally effective. In children, it is usually given at 4-8 mg/kg/day. Acute toxic effects such as ataxia and nystagmus are dose related and frequent. Chronic adverse effects such as gingival hyperplasia, hirsutism and coarsening of facies should be taken into consideration, particularly in the case of children. Neuropathy and cerebellar degeneration may occur with long-term use. [14]

PHT was approved in the USA in 1953 as first-line and adjunctive therapy for treatment of FS and generalized seizures, except myoclonic and absence seizures. [15]

Diazepam

It was the first benzodiazepine to be used in epilepsy. Occasionally, it is given as a long term anti-epileptic. It is used as an adjunctive therapy in severe partial and generalized epilepsy and in Lennox-Gastaut syndrome; the recommended dose is 0.25-1.5 mg/kg/d. Diazepam rectal gel is effective in preventing subsequent seizures during seizure clusters [16-18] and in pediatric status

epilepticus [19] and can reduce the frequency of emergency department visits. [20] Rectal diazepam is also given at the time of fever in febrile seizures.

Ethosuximide (ETS)

Ethosuximide is a succinimide anticonvulsant, used mainly in absence seizures. The drug is a T-type calcium channel blocker in the thalamus and this is the mechanism against absence seizures. It is approved for absence seizures. Therapy with ethosuximide in children can be initiated at a dose of approximately 10 mg/kg/day. The dose can be titrated up at intervals of 5-7 days as necessary and as tolerated, up to a dose of approximately 30-40 mg/kg/day.

Gastrointestinal side effects occur frequently and include anorexia, nausea and vomiting, cramps, epigastric and abdominal pain, weight loss and diarrhea. Otherwise it is practically free of serious side effects. [21]

ETS was approved in the USA in 1970 as first-line and adjunctive therapy for treatment of generalized absence seizures. [22]

Phenobarbitone

Phenobarbitone was recommended by the World Health Organization (WHO) as the first-line agent for the control of seizures, [23] but this has been contested on the grounds that it is biased against resource-poor countries. [24] It was first used as an anticonvulsant in 1912, but now has little role to play in First-World countries where the newergeneration agents are readily accessible. Phenobarbitone monotherapy has equivalent efficacy to the newer anticonvulsants (phenytoin, sodium valproate and carbamazepine) in children with partial-onset and generalised tonic-clonic seizures. [25]

Phenobarbitone is cheap, readily available, and easy to use and store. However, it has definite cognitive and behavioural side-effects in many children. It can exacerbate seizures in about 35% of children, and extreme caution should be taken with children who have a pre-morbid state of behavioural problems or attention deficit hyperactivity disorder (ADHD). [26]

Valproate

Valproate is broad spectrum AED and has stood the test of time; it can be used in all types of seizures. Valproate increases the synaptosomal GABA concentration through the inhibition of GABA transaminase. Valproic acid is the drug of choice in idiopathic generalized epilepsy. Open and comparative studies have shown excellent control rates in patients with newly diagnosed typical absence seizures. It is the drug of choice for juvenile myoclonic epilepsy and can be used in other types of myoclonus. Moreover, it is the first-line drug in photosensitive epilepsy and Lennox-Gastaut syndrome. It is a second choice in the treatment of infantile spasms. In focal epilepsy also, it has been shown to be as effective as other first-line agents. It has been shown to be clearly effective in preventing the recurrence of febrile seizures. [27] In children, the usual starting dose is 20 mg/kg/day and the maintenance dose is 40 mg/kg. IV valproic acid should be administered as a 60 min infusion with a rate not exceeding 20 mg/min. It is contraindicated in patients with hepatic dysfunction and mitochondrial disorders. Common side effects are dyspepsia and/or weight gain. Less common are peripheral edema, dizziness, drowsiness, hair loss, sedation and tremors. It can cause potentially fatal hepatotoxicity mostly in infants younger than 3 years of age and in patients on polytherapy. [28] Children may develop nocturnal enuresis. [29]

Felbamate

As with most anticonvulsants, the precise mechanism is unknown. It has a weak inhibitory effect on GABA receptor binding sites. Felbamate is not indicated as a first-line antiepileptic treatment. It is recommended for use only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use. It can be considered for either monotherapy or adjunctive therapy in the treatment of partial seizures, with or without generalization, in adults with epilepsy and as adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox- Gastaut syndrome in children. Uncontrolled observations have suggested that it may be effective against absence seizures, [21] infantile spasms [30-32] and acquired epileptic aphasia. In children, the recommended dose is 15 mg/kg/day with weekly increments up to 45-80 mg/kg/day. Adverse reactions involve decreased appetite, vomiting, insomnia, nausea, dizziness, somnolence and headache. Two rare but life threatening adverse effects such as aplastic anemia and hepatic failure has limited its use to severe refractory epilepsies. [33]

Lamotrigine

Lamotrigine is a broad spectrum AED. It is thought to act by blocking voltage-sensitive sodium channels to stabilize neuronal membranes and inhibit the release of excitatory amino acid neurotransmitters. It is effective as both the add-on therapy and monotherapy in partial seizures, primary generalized seizures, atypical absence seizures, tonic/atonic seizures and Lennox-Gastaut syndrome. It is sometimes effective for myoclonic seizures but can cause the worsening of myoclonic seizures in some patients. In monotherapy, 25 mg is given for 2 weeks, than 50 mg for 2 weeks, followed by a maintenance dose of 100-400 mg/day in two divided doses. Valproate strongly interferes with the metabolism of lamotrigine, thereby producing a marked elevation in its blood levels so that lower doses have to be used. In children on Valproate, the starting dose is 0.15 mg/kg; with concomitant enzymes inducers, the starting dose is 0.6 mg/kg, and as monotherapy, it is initiated at 0.4 mg/kg/day. Rash (5%) is the main concern associated with this drug. Severe rash may develop and lead to Stevens-Johnson syndrome, which may be fatal but rare (0.1%). Other commonly reported adverse reactions are headache, blood dyscrasias, ataxia, diplopia, GI disturbances, psychosis, tremors and somnolence.

Levetiracetam

Levetiracetam is the S-enantiomer of the ethyl analog of piracetam. It binds selectively to a synaptic vesicle protein known as SV2A and exactly how binding confers antiepileptic action is unclear. It is effective as the add-on therapy for refractory partial-onset seizures. It is also effective in generalized epilepsies. In open label trials, adult patients with chronic cortical myoclonus were successfully treated with levetiracetam. In pediatric patients of more than 4 years of age, the treatment should be initiated with 20 mg/kg/day in two divided doses and increased every 2 weeks by 20 mg/kg up to 60 mg/kg/day. It is not approved for children below 4 years of age. It is a relatively well tolerated drug. The common side effects are dizziness, somnolence, asthenia and infection. Increasing behavioral problems are being recognized particularly in children. [34, 35]

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

CONCLUSION

It is important to treat epilepsy for several reasons. Untreated epilepsy places paediatrics at increased risk of accidents, such as drowning, head injury from a fall, or choking. Frequent seizures may create both social and academic disadvantages for children. Antiepileptic drug should only be introduced when a firm diagnosis of epilepsy has been made. One of the main considerations of whether to start treatment is the chance of seizures recurrence.

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CONFLICT OF INTEREST REPORTED: NIL ; SOURCE OF FUNDING: NONE REPORTED