Invited Review

Antiepileptic drugs in pediatric epilepsy

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ABSTRACT

The epilepsies are socially handicapping disorders and even a single seizure occurring in certain circumstances may have disastrous effect. 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. Drug treatment is the major form of therapy for a vast majority of children with epilepsy. The choice of antiepileptic drugs (AEDs) in a child depends on the type of seizures, syndrome diagnosis, age of the patient and its consequent adverse effects. The metabolism of AED also differs according to the pediatric age group, requiring different dose regimens. Here, a brief review of AED used in the pediatric age group is presented.

Key words: Antiepileptic drugs, epilepsy, seizure

Introduction

It is estimated that 0.5-1% of children have epilepsy.[1] In spite of the recent advances in pharmacologic therapy and the development of an improved classification system, 25% of children who are diagnosed with epilepsy remain refractory to traditional therapy.[2] Pediatric epilepsy differs from adult epilepsy in terms of the etiologies, response to treatment and the level of impact of the illness on the patient and the family. Antiepileptic drugs (AEDs) as well as seizures are known to affect learning, schooling, social development and behavior. Twenty to thirty percent of children with epilepsy have learning difficulties. A careful and detailed assessment is required to tailor the treatment and educational programs.

Seizures affect the personality and interfere with schooling and choice of career. Overall support for the child is an important aspect of management.

General Guidelines

Drug treatment forms one of the most important forms of therapy for a vast majority of epilepsy patients. Clinical experience has shown that AEDs can control high proportion of cases of epilepsy. However, there are certain general principles or guidelines should be followed to get the best results of medical management. Clinical practice has shown that a precise diagnosis when combined with better understanding of the mechanisms of action of AEDs gives the most effective use of drug treatment. Various factors like age of onset, seizure type and frequency, electroencephalography (EEG) and imaging results, etc. enable the neurologist to reach a precise syndromic diagnosis and to select the most appropriate AEDs for individual patient. Treatment is a reasonable compromise between benefits and toxicity, i.e., between control of seizures and side effects. It is important to explain to the patient and family members that various drugs may have to be used at various dosages to reach the best possible drug with appropriate dose. This will increase their cooperation during this chronic treatment. Whenever possible, the initial drug choice must be based on a specific syndromic diagnosis.[3] The treatment is always long-lasting, ranging from a minimum duration of 1 to 2 years to life-long. All antiepileptic agents produce side effects that may seriously hamper the patient's activities. The cognitive effects of anticonvulsants[4] are particularly worrying and no drug appears to be completely exempt from unfavorable cognitive or behavioral effects, even though these may be more marked with some agents (e.g., phenobarbitone) than with others (e.g. sodium valproate, carbamazepine, lamotrigine). The relative side effects of the newer AEDs are yet to be fully determined. The word-finding difficulty observed in both children and adults is unique to topiramate.[5] During the last 20 years, the use of a single drug (monotherapy) has been preferred to polypharmacy. Several studies have shown that 70-90% of newly diagnosed common forms of epilepsy can be controlled using a single agent.[6]

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The use of single agent is generally associated with side effects that are fewer and easier to recognize than polypharmacy and the opportunity for drug interaction is lower. In case of failure of the first drug, substitution with another drug is preferable to the addition of another drug. However, before this, the plasma level may have to be verified before switching to another drug. When control is obtained after the addition of the second drug, the withdrawal of the first agent may be attempted to verify that the second drug rather than a combination of both was actually the effective agent. No consensus exists on the number of monotherapy trials that should be attempted before the combination therapy is introduced; however, at least two appropriate AEDs at maximally tolerated dose must be used. Many physicians systematically adjust the dose until it is within the so-called "optimal range" of blood levels. However, keeping the dose as low as possible is preferable, as long as the clinical control is gained, even if the blood levels remain "subtherapeutic". However, physicians must be aware that, even when the drug is used within the so-called therapeutic range, the control of seizures is the sole criterion of efficacy. Most recurrences occur within 3 months of the first seizure; patients who have had no fit during that period can probably be maintained on a low dose, regardless of the blood levels. However, if no side effects develop in the absence of control, the recommendation is to increase the blood levels above the so-called therapeutic range, provided this is done with caution and proper surveillance. Increasing the doses of AEDs to the highest possible level is perhaps safer with the newer antiepileptic agents such as lamotrigine and gabapentin. Ineffective drugs should be withdrawn progressively over 1 to 3 months. Thus, for a brief duration, the two drugs are administered simultaneously. In focal epilepsies, it is now common practice to consider surgery after two or three drugs have failed. To clearly establish the lack of efficacy of drug, serum levels have to be done before it is abandoned.

Here, there is a brief review of various old as well as new AED used in pediatric epilepsy. The pharmacokinetics of AED is given in Table 1. The AEDs used in various types of epilepsy is cited in Table 2.

Table 1: Main pharmacokinetic data on anticonvulsant drugs

Drug	Oral bioavailability*	Tmax (h)*†	Protein binding (%)*	Plasma half-life (h)	Apparent VD (L/kg)	Optimal range‡ (ug/ml)	Optimal range‡ (umol/l)
Acetazolamide	>90	1-3	90-95	10-12	1.8	10-14	NA
Carbamazepine	75-85	2-24	70-80	35.6 ± 15.3‡§	1.20 ± 45	4-12	17-51
Clobazam	87	1.3-1.7	82-90	16-48.6	194 (ch)	NA	NA
Clonazepam	95	2-3 (ch)	86	28 ± 4.6 (ch)	2.1 ± 0.6 (ch)	NA	NA
Diazepam	75	1-2	95	10-20	2.6 ± 0.5 (ch)	NA	NA
Ethosuximide	100	1-4	0	30	0.7	40-100	300-750
Felbamate	NA	NA	22-25	16-22	0.756	NA	NA
Fosphenytoin	NA	0.97 ± 1.8	95-99	0.25	0.04	NA	NA
Gabapentin	35-57	2-3	0	5-7	50-58	NA	NA
Lamotrigine	70	2-4	55	19-30"	0.9-1.5	NA	NA
Levetiracetam	>95	1.3	0	5-7 (ch)	0.5-0.7	NA	NA
Oxcarbazepine	89	1.3 ± 2	60	3.1 ± 1.5	11.5	NA	20-200
Phenobarbital	80	2-10	50	37-73	0.9	10-30	45-130
Phenytoin	80-95	4-12	90	20	0.65	10-20	40-80
Primidone	90	0.5-2	10	5-10	0.6-1	5-12	23-55
Tiagabine	>90	0.5-2	>95	4.5-8.1	NA	NA	NA
Topiramate	81-95	1-3	9-17	21	40-60	NA	NA
Valproate	100	1-3‖	90	7-15	0.2	50-100	345-690
Vigabatrin	60-80	1-4	0	0.6-10	5-7	NA	NA
Zonisamide	NA	2.4-5.8	40-60	50-88	1.8	NA	NA

ch - children; NA - not applicable in clinical practice; Tmax - time of maximal concentration; VD - volume of distribution, *The protein binding data of various AEDs is mainly from adult studies, †Time to maximum blood level following a single dose, ‡Indicative value only, §Higher figure value for single dose, ‖Enteric-coated preparations have an average Tmax of 6-8 h, "Considerably prolonged when combined with Valproate; decreased when combined with inducers

Table 2: Main drugs for various types of epilepsy

Type of epilepsy	Drugs
Idiopathic generalized epilepsies with tonic-clonic seizures	*Valproate*, lamotrigine, topiramate, phenytoin, phenobarbital
Generalized epilepsies with myoclonic seizures	*Valproate*, lamotrigine, Topiramate, ethosuximide, phenobarbital, clonazepam
Generalized epilepsies with typical absences	*Valproate*, ethosuximide, lamotrigine, benzodiazepines
West syndrome	*Vigabatrin*, ACTH and/or corticosteroids, nitrazepam, valproate
Idiopathic partial epilepsies	*Valproate*, carbamazepine, levetiracetam, zonisamide
Symptomatic partial seizures	*Carbamazepine, valproate*, topiramate, levetiracetam, zonisamide, lamotrigine
Continuous spike-waves of slow sleep (electrical status epilepticus of slow sleep and Landau-Kleffner)	*Clobazam*, ethosuximide, ACTH and/or corticosteroids, immunoglobulins, valproate
Dravet syndrome	*Valproate*, clobazam, stiripentol, topiramate

The drugs usually considered as the first choice are in italic type. The order of preference is only approximate and depends on various factors

Carbamazepine

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.[7] 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 hepatic 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.

Oxcarbazepine

Oxcarbazepine is an anticonvulsant and mood stabilizing drug, used primarily in the treatment of epilepsy and bipolar disorder. It is structurally a derivative of carbamazepine. It is thought to have same mechanism as carbamazepine-sodium channel inhibition. Unlike carbamazepine, it is completely absorbed after oral ingestion. There is no autoinduction. It has the advantage of not inhibiting or inducing hepatic microsomal enzymes to the same extent as carbamazepine. It is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and as a monotherapy in the treatment of partial seizures in children aged 4 years and above with epilepsy. In children, the recommended initial dose is 5-10 mg/kg/day. This dose can be increased weekly by increments of 5-10 mg/kg/day, to up to 20-30 mg/kg/day. The side effect profile of oxcarbazepine is similar to that of carbamazepine, but there are minor differences. Leucopenia is less common and the monitoring of the blood count is not necessary. However, hyponatremia may be more common than with carbamazepine.[8]

Clobazam

This benzodiazepine is unique in having 1,5 substitution instead of the usual 1,4-diazepine. This change results in an 80% reduction in its anxiolytic activity and a 10-fold decrease in its sedative effects. In addition to its agonist action at the GABA-A receptor, clobazam may affect the voltage-sensitive conductance of calcium ions and the function of sodium channels. It is used as an adjunctive therapy in a broad spectrum of epilepsies, although it is best in partial epilepsies. The major clinical problem of this drug is the development of tolerance and loss of initial effectiveness in few weeks to months. This is probably due to downregulation of benzodiazepines receptors in the brain. This also accounts for withdrawal seizures. The maintenance dose is between 0.5 and 1 mg/kg/day. Essentially, the side effects are similar to those of other benzodiazepines. The most common is sedation. Other adverse effects include dizziness, lack of coordination, irritability, depression and muscle fatigue. Therefore the use should more often be short term to cover the periods of increase seizure susceptibility such as change over of AEDs and during perimenstural period.

Clonazepam

Clonazepam is one of the first benzodiazepines used for epilepsy. It has higher affinity for the GABA-A receptor site than diazepam and binds to subgroups of GABA-A receptors that do not bind with other benzodiazepines. It is mainly used in treatment of generalized epilepsies such as absence epilepsy, tonic-clonic seizures, myoclonic seizures and subcortical myoclonus. It is also relatively safe in acute intermittent porphyria. In children, it is used as an adjunct in the treatment of various generalized epilepsies including absence seizures. It is also used as a secondary drug in infantile spasms and myoclonic seizures. It is started with initial dose of 0.01 to 0.03 mg/kg/day and increased at intervals of one week up to 0.1 to 0.3 mg/kg/day into 2-3 divided doses. The most common side effects are referable to CNS depression. Drowsiness occurs in approximately 50% of patients and ataxia in approximately 30%. Behavioral problems have been noticed in approximately 25% patients. Because of the possibility that adverse effects on childhood mental development could become apparent only after years, a risk-benefit consideration of the long-term use of clonazepam is important in pediatric patients.

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[9-11] and in pediatric status epilepticus[12] and can reduce the frequency of emergency department visits.[13] Rectal diazepam is also given at the time of fever in febrile seizures.

Ethosuximide

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.

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,[14] infantile spasms[15-17] and acquired epileptic aphasia.[18] 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.

Phenytoin

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 build up 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.[19] 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.[20] In children, it is usually given at 4-8 mg/kg/day. Phenytoin is metabolized by hepatic P450 enzyme system and first step involves zero order kinetic accounting for nonlinear relation of dose: serum level. After the point of enzymatic saturation, the further increase in the dose leads to steep increase in the plasma levels. It can be administered intravenously but not intramuscularly as it can cause muscle necrosis. 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.

Fosphenytoin

Fosphenytoin is a phosphate ester prodrug of phenytoin. As it is a prodrug of phenytoin and accordingly its anticonvulsant effects are attributable to phenytoin. The modulation of sodium channels may be a primary anticonvulsant mechanism. It is water soluble and prepared in Tris buffer, it thus causes less thrombophlebitis than phenytoin when administered intravenously and can also be administered intramuscularly. The advantage over phenytoin is that it can be administered three times faster than phenytoin and the local side effects are considerably less. Fosphenytoin is approved in the United States for a short term (five days or less) treatment of epilepsy when more widely used means of phenytoin administration are not possible or ill-advised, such as endotracheal intubation, status epilepticus and other types of repeated seizures. The dosages are expressed as phenytoin equivalents (PE). The loading dose of fosphenytoin is 10-20 mg PE/kg given IV or IM. The rate of administration for IV fosphenytoin should not be greater than 150 mg PE/min and the maintenance dose can be 4-6 mg PE/kg/day. Drug is not recommended for children under 5 years of age. Side effects are similar to phenytoin, except that fosphenytoin causes less hypotension and more paresthesia. Fosphenytoin can cause hyperphosphatemia in end-stage renal failure patients.

Gabapentin

Gabapentin was thought to mimic the actions of GABA; however, later evidence did not prove this. It appears to bind to a calcium channel receptors in cerebral neocortex and hippocampus, but the exact mechanism is uncertain. It is indicated as adjunctive or monotherapy in the treatment of partial seizures. In children, the starting dose should range from 10-15 mg/kg/day in three divided doses and effective dose is 25-35 mg/kg/day. In infants and children, the dosage should be higher by 33% than that for older children. Children with the age of 3-12 years were also observed to be susceptible to mild to moderate mood swings, hostility, concentration problems and hyperactivity. Other common side effects are somnolence, dizziness, ataxia, nystagmus, tremor, headache and fatigue. Although rare, there are several cases of hepatotoxicity reported in the literature. It should be used carefully in patients with renal impairment due to possible accumulation and toxicity.

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.[21,22] In four children with epilepsy, reversible psychosis with visual and auditory hallucinations developed after its introduction.[23]

Phenobarbital

Phenobarbital is one of the oldest and cheapest AED. It binds strongly to GABA-A receptors and increases the duration of channel opening. At a higher concentration, it also reduces sodium and potassium conductance. It causes cognitive impairment in adults as well as in children; therefore, its use is markedly reduced. However, it is still used in developing countries, particulary in low profile patients. It is indicated in the treatment of all types of seizures except absence seizures. Phenobarbital is the first-line choice for the treatment of neonatal seizures. It can also be effective in the treatment of juvenile myoclonic epilepsy, but it is not the preferred drug. In children, the starting dose is 3 mg/kg/day and the dosage is maintained between 3 and 6 mg/kg/d. Discontinuation should always be gradual over several weeks because of risk of withdrawal seizures. Sedation and hypnosis are the principal side effects in addition to cognitive impairment. CNS effects such as dizziness, nystagmus and ataxia are also common. In elderly patients, it may cause excitement and confusion, whereas in children, it may result in paradoxical hyperactivity. Long-term usage of drug can be associated with the coarsening of facial features, osteomalacia, Dupuytren contractures and cerebellar atrophy.

Primidone

In the body, it is converted into phenobarbital; therefore, its spectrum of efficacy and side effects are very similar to phenobarbital. It has been evaluated as adjunctive therapy in neonates with seizures and found to be effective.[24,25] In children, it is initiated in dose as low as 1-2 mg/kg and increased at intervals of 3 days to 10-20 mg/kg/day. Primidone can cause intense dizziness, nausea and sedation that commonly occurs at the onset of therapy, sometimes after only one tablet and it is advisable to start with a very low dose. Other side effects are similar to Phenobarbital.

Tiagabine

It is one of the newer AEDs and is also used in the treatment for panic disorder. It appears to operate as a selective GABA reuptake inhibitor. It is used as second-line add-on therapy in patients with partial and secondarily generalized seizures refractory to treatment. The drug is recommended as an adjunctive therapy for the treatment of partial seizures in patients who are 12 years and older. The drug should be initiated at 4 mg/day and increased by 4-8 mg/day each week and the usual maintenance dose is 32-56 mg/day. Most common side effects include confusion, difficulty in speaking, mild sedation, tingling sensation in the extremities, particularly the hands and fingers. At least, five cases of nonconvulsive status epilepticus have been attributed to tiagabine.[26,27]

Topiramate

Topiramate is an anticonvulsant drug which is used to treat epilepsy in both children and adults. It is also approved for the prevention of migraines. It enhances GABA-activated chloride channels, inhibits excitatory neurotransmission through action on kainite and AMPA receptors, modulates sodium channel conductance and inhibits brain carbonic anhydrase. It is recommended for partial onset seizures or primary generalized epilepsy in polytherapy and as monotherapy in both children and adults. It is also useful in Lennox-Gastaut syndrome. In children, the starting dose is 0.5-1 mg/kg/day with increments of 0.5-1 mg/kg/day every one week until the maintenance dose of 4-6 mg/kg/day is reached. The side effects include change in taste, paresthesias, cognitive impairment, psychomotor slowing, impaired concentration and language difficulties.[28,29] Language difficulties are more common if there is a left temporal lesion. Other side effects include anorexia, renal stones, metabolic acidosis[30-32] and weight loss. Recently, acute angle glaucoma has been reported.

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.[33] 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.[34] Children may develop nocturnal enuresis.[35] It also causes hyperammonemia, blood dyscrasias, impaired liver function, jaundice, thrombocytopenia. Treatment with valproic acid during the first trimester of pregnancy has found to be associated with an estimated 1-2 percent risk of the neural tube defect in the newborn.[36,37] Polycystic ovarian syndrome has been particularly associated with valproate therapy so it should be given cautiously in adolescent girls.

Vigabatrin

Vigabatrin is an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the catabolism of GABA, which increases the level of GABA in the synapses. It is the drug of choice for infantile spasms. It is less effective against primary generalized tonic-clonic seizures and may worsen myoclonic seizures or generalized absence seizures. It has been reported to cause absence status. An add-on study was carried out in a total of 70 patients with infantile spasms.[38] A seizure reduction of at least 50% was observed in 68% of the patients and 43% became seizure free. Several other studies have documented the efficacy of Vigabatrin as a first drug in treatment of infantile spasms, particularly among those with structural brain anomalies and tuberous sclerosis.[39-43] In children, 40 mg/kg/day is the usual starting dose, with a maintenance dose of 80-100 mg/kg/day. Doses of 100-200 mg/kg/day may be necessary in infants treated for infantile spasms. The response to infantile spasms is observed in 1-2 weeks; later, it can be continued only for few months to reduce the chances of visual field defect. It must be discontinued slowly to avoid rebound seizures. Main side effects are sedation, agitation, insomnia, depression, weight gain. There is frequent (20-40%) occurrence of irreversible visual field constriction.[44] Most patients are subjectively asymptomatic. This effect has also been documented in children.[45,46] It may exacerbate seizures, predominately among patients with non-progressive myoclonic epilepsy and the Lennox-Gastaut syndrome.[44,47] It was also found to exacerbate absence seizures[48] and seizures in patients with Angelman syndrome.[49]

Zonisamide

The exact mechanism of action is not known. According to Leppik, zonisamide may be a carbonic anhydrase inhibitor such as acetazolamide; but the primary mechanism of action might be the blocking repetitive firing of voltage-gated sodium channels and reduction in T-type calcium channel currents or by allosterically binding to GABA receptors such as the benzodiazepines or by increasing the levels of the glutamate transport protein in the brain, while decreasing the amount of GABA transport protein. In other words, the uptake of the inhibitory neurotransmitter GABA is inhibited when the uptake of the excitatory neurotransmitter glutamate is enhanced. Zonisamide is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy. In addition, there have also been reports that suggest successful treatment in patients with various generalized seizures such as generalized tonic-clonic seizures, absences and infantile spasms[50-52] as well as in early infantile epileptic encephalopathy.[53] It appears to have a specific indication in progressive myoclonic epilepsy, such as Unverricht-Lundborg disease[54,55] and Lafora disease.[56] The recommended initial dose in children is 1-2 mg/kg/day, which is increased by 1-2 mg/kg/day at intervals of 1-2 weeks, to a target dose of 4-8 mg/kg/day and a maximum of 12 mg/kg/day. The most common side effects include somnolence, loss of appetite, dizziness and ataxia. Psychotic reactions have also been observed.[57] Nephrolithiasis can be associated with treatment and seems to occur more frequently in the USA and in Europe then in Japan.[58,59] It can also cause oligohidrosis.[60,61]

Acetzolamide

Acetzolamide is a sulphonamide derivative, and it acts as an antiepileptic probably by inhibiting the carbonic anhydrase enzyme. It is effective in both generalized seizures as well as partial and secondary generalized seizures. It has an initial effect in almost all the patients, but the effect diminishes with time as the tolerance develops over 3-6 months; however, drug holiday will restore its efficacy. It is usually given as an adjunctive therapy in severe epilepsy when other more conventional therapies have failed. The usual dose in children is 10-30 mg/kg/day. In catamenial epilepsy, it is started few days prior to onset of menses and continued for few days subsequently. Similar to any sulphonamide drug, it can also cause acute hypersensitivity. It also causes anorexia, drowsiness, paresthesias, diuresis, metabolic acidosis and renal calculi.

Adrenocorticotropic Hormone (ACTH) and Steroids

Although they have a clear antiepileptic action, the mechanism of action is still not clear. Adrenocorticotropic Hormone is mainly used in the treatment of West syndrome. Moreover, it is used in refractory epilepsies such as Lennox-Gastaut syndrome and in Landau-Kleffner syndrome. The indication of steroids is same as that of ACTH, and the steroids seem have an equal efficacy; however, some pediatricians prefer ACTH. Snead recommends the following regimen: 150 u/m^2/day for 1 week, followed by 75 u/m^2/day for another week and then same dose on alternate days for 2 weeks.[62] Then, it is gradually tapered over 8-9 weeks. In infantile spasms, ACTH is effective in 70-75% of children and in Lennox-Gastaut syndrome, it is effective in 40-60%. ACTH does not significantly alter the course of these patients. Children in India should be screened for tuberculosis before starting ACTH. Most children develop behavioral changes such as irritability and Cushingoid features. It can also cause hypertension, infections, hypokalemia, hyperglycemia and congestive heart failure.

Pyridoxine

Pyridoxine dependency, an autosomal recessive inborn error of metabolism, does not have characteristic clinical features and it should be considered in any child with cryptogenic refractory seizures up to the age of 2 years, including those with infantile spasms.[63] The diagnosis can be established by administering 50-100 mg of pyridoxine intravenously during a flurry of seizures. If there is a good response within minutes to hours, then the diagnosis of pyridoxine deficiency is confirmed. These children can then be administered with an oral maintenance dose of 50-100 mg/day. The use of very high dose of pyridoxine (200-400 mg/kg/day) in patients with infantile spasms has been advocated.[64]

Rational Polytherapy

It is preferable to use combinations of drugs with different mechanisms of action.[65] An agent that primarily acts on membrane conductance, such as carbamazepine, should therefore be combined with one that has a predominately synaptic mechanism of action, such as sodium valproate. In general, care should be taken to avoid certain combinations, particularly the association of drugs that have similar side effects that may be additive when used together. For example, phenobarbital and clonazepam may produce marked sedation. Similarly, combining phenobarbital with drugs such as primidon that are metabolized in large part to phenobarbital is not wise. Combinations of three or more drugs are only rarely indicated and their efficacy remains to be demonstrated.[66] For patients on polytherapy, frequent drug levels are advisable because of possible drug interactions.

Monitoring of AED Treatment

Since epilepsy is a chronic disorder, long-term monitoring is required. Search for side effects may be difficult in infants or mentally retarded children. Slowing or decrease in school performance could be due to the maladjustment to drugs.

As the long-term side effects and toxicity of AEDs in developing children are largely unknown and subtle effects may occur even at normal drug level, using the lowest possible dose of AEDs that controls seizures, irrespective of the plasma levels is strongly recommended.

When toxicity is suspected, blood sampling at time of likely maximal level is best. If ineffective treatment is suspected that sampling at time of likely trough level is recommended.

EEG has only secondary role in the regulation of the drug treatment as the objective should be to control clinical seizures and not the complete suppression of epileptiform activity on EEG.

Discontinuation of Drug Treatment

Matricardi *et al.* followed 425 children who were seizure-free for 2 years for an average of 8 years.[67] Eighty-eight percent remained seizure free. Relapse rate was 11% in mentally normal children and 21% in mentally retarded children.

Factors associated with multiple relapses are structural brain abnormality, need for more than one AED, grossly abnormal EEGs, progressive epileptic encephalopathy, mental retardation. Most authors think that 2 years seizure-free period could be sufficient in majority. However, in syndromes such as juvenile myoclonic epilepsy (JME) and lennox gastaut syndrome (LGS), severe myclonic epilepsy treatment has to be continued for a long period.

Normal EEG is not a prerequisite for discontinuation of AEDs, particulary in syndromes such as Benign Rolandic Epilepsy.

Antiepileptic drug withdrawal should always be carried out over 6 months to 1 year and never abrupt. Fits that occur 2-3 months after the withdrawal should be regarded as relapse and the resumption of treatment for a long period is then generally indicated. Surgery has become a more accessible solution for a growing number of patients, and in cases of partial epilepsy, it should be considered as an early option.

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Source of Support: Nil, **Conflict of Interest:** None declared.