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Leading Article

Use of New Generation Antiepileptic Drugs in Children

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Aim of epilepsy management is to cure seizure and to maintain a good quality of life[1]. Quality of life is affected not only by the epileptic attacks but also by the adverse effect of the drug. This concern is more in case of developing brain of children[1]. However, due to many reasons, selection of antiepileptic drug is a challenging task. During selection of a drug, three important drug properties need to be considered: efficacy, tolerability and safety.

In the recent past, better understanding of the epileptogenesis and mechanism of action of drugs & their toxicities have helped in the development of new generation antiepileptic drugs (AEDs) which are effective as well as safer & better tolerable than older AEDs. The new generation AEDs are either approved and used widely or on clinical trial[1,2].The introduction of these drugs, has increased the treatment options for children and adolescents with epilepsy, especially in refractory cases[3]. Many have gained widespread usage as monotherapy and adjunctive treatment[1].

The committee of the American Academy of Neurology recommends that the new AEDs may be better tolerated than the standard older generation AEDs[4, 9]. However, newer AEDs pose a specific challenge in the pediatric population, as these are usually approved based on clinical trials involving mainly adults[2]. Issues, specific to children such as tolerability, organ specific toxicity and the effect on development, behavior and cognition remain undetermined. A brief account of the time of approval, mechanism of action and side effects of the new AEDs are shown in table-I.

Table-I

The new generation antiepileptic drugs :Mechanisms of action and side effects[2,3]

AED name	Time of approval	Mechanism(s) of action	Important Side effects
Vigabatrin	1989	Inhibits GABA-T; stimulate GABA release	Headache, drowsiness; visual field deficits.
Felbamate	1993	Inhibition of voltage –gated sodium channels	Fulminant hepatic failure and aplastic anemia
Gabapentin	1993	Inhibition of voltage- sensitive calcium channels.	Somnolence, weight gain
Lamotrigine	1994	Blocks sodium channels; inhibits calcium currents.	Hypersensitivity reactions, Stevens Johnson syndrome
Tiagabine	1997	Enhances GABA mediated inhibition by blocking GABA reuptake.	Tremor, abdominal pain, psychosis
Topiramate	1997	Blocks voltage-activated sodium channels; enhances GABA activity, reduces calcium currents; activates potassium conduction.	Metabolic acidosis, oligohydrosis, Renal calculi, hepatic failure; impaired language fluency and cognition, weight loss.
Levetiracetam	1999	Binds SV2A, a presynaptic protein on synaptic vesicles.	Irritability, behavioral problems.
Oxcarbazepine	2000	Blocks voltage-dependent sodium channels and calcium channels.	Rash hyponatremia, Stevens Johnson syndrome.
Zonisamide	2000	Blocks calcium channels, inhibits sodium channels and glutamate release.	Anorexia, Rash, Stevens Johnson syndrome, renal calculi, aplastic anemia, oligohydrosis.
Rufinamide	2008	Inhibits voltage- dependent sodium channels.	Anorexia headache.
Lacosamide	2009	Inhibits sodium channels.	Headache, diplopia.

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According to International League Against Epilepsy, oxcarbazepine (OXC) has superior efficacy in partial onset seizure in children[2-4]. OXC is easy to use due to lack of auto induction which creates problem in carbamazepine (CBZ) use[1]. OXC is better tolerated and has fewer drug interactions compared to CBZ[1]. Vigabatrin is the drug of first choice in treating infantile spasm with tuberous sclerosis[2]. Lamotrigine (LTG) is effective in partial seizures, primary generalized tonic-clonic seizures, childhood absence epilepsy, Lennox–Gastaut syndrome, juvenile myoclonic epilepsy[5,6]. LTG does not induce or inhibit hepatic enzymes[2]. Levetiracetam is effective as monothrapy and adjunctive therapy in treating idiopathic generalized epilepsy in children including childhood absence seizure and juvenile myoclonic epilepsy and a wide variety of epileptic syndrome. Levetiracetam is not involved in induction or inhibition of hepatic enzymes & excreted mostly unchanged in urine. It does not interact significantly with other antiepileptic drugs. It is very useful in patients with hepatic or renal insufficiency and in patients on concomitant medications[7].

Topiramate is effective in childhood partial, generalized seizures, Lennox- Gastaut syndrome, West syndrome, juvenile myoclonic epilepsy, childhood absence epilepsy, Doose syndrome, severe myoclonic epilepsy of infancy, and progressive myoclonic epilepsies[8].Topiramate generally does not affect the steady state concentrations of the other drugs given in polytherapy[2].

Zonisamide has beneficial effects on partial seizures with secondary generalized seizures, idiopathic and symptomatic generalized epilepsies[9]. Zonisamide has no major effects on plasma level of concomitant AEDs[1].

However, there is no specific roadmap for the use of AEDs in children. Evidence based medicine and expert opinion help to provide guidelines for their use. The task of choosing an AED for a child requires a thorough knowledge of the proposed mechanism of action, pharmacokinetics in children, age specific side effects and effects on the developing brain. It also requires a tailored approach to each patient taking into account the age, underlying etiology, epileptic syndrome, adjunctive AEDs that the patient is receiving, available formulations, coexisting medical problems and behavioral profile[1-3].

In conclusion, the modern era has witnessed important advances in antiepileptic drugs either through development of novel molecules or targeted structural improvement of older antiepileptic drugs. Evidence from randomized controlled trials involving paediatric population is essential. This will help to formulate evidence based guidelines to use new antiepileptic drugs.

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