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Editorial

Improving Pediatric Care for Epileptic Children - What Does the Pediatrician Needs to Know about Antiepileptic Drugs?

While sharing a common property of suppressing seizures, antiepileptic drugs (AEDs) have many different pharmacological profiles that are relevant when selecting and prescribing these agents in children with epilepsy and other conditions. This includes pharmacokinetic properties, drug-drug interactions, and side effect profiles and toxicities [1]. Over the past two decades, the number of AEDs has more than doubled. Unlike some of the former AEDs such as phenobarbital and phenytoin, many of the currently AEDs have simple pharmacokinetics and less side effects on liver. This explains into a generally lower rate of side effects, reduced need for serum monitoring, once or twice daily dosing and fewer drug-drug interactions. Despite these advantages, however, there are few data to suggest significant differences in effectiveness among the older AEDs [1,2].

After a first unprovoked seizure, the chances of a second seizure range from 30 to 55% over the next 2-5 years. Mostly a developmentally normal child with first idiopathic generalized tonic clonic seizure does not require long term AEDs [2,3]. After a second

unprovoked seizure, the chances of a third unprovoked seizure are 80 to 90% within 2 years if treatment is not initiated. Therefore, treatment after the second unprovoked seizure is recommended [3]. There is no ideal AED. In most cases it has to be individualized. The AED of choice depends on the classification of the seizure, determined by the history and EEG findings. The goal for every patient should be the use of only one drug with the fewest possible side effects for complete seizure control and the best quality of life. The drug is increased slowly until seizure control is accomplished or until undesirable side effects develop. Monotherapy in appropriate dose controls seizures in 70-80% cases. If seizures are uncontrolled with the first drug, choose alternate monotherapy and gradually withdraw the first drug. If seizures are still not controlled, refer to a child neurologist. The patient may require polytherapy, ketogenic diet or surgery. Before labeling drug failure, always check compliance; rule out conditions that mimic epilepsy and progressive neurological disorders. Pediatricians should be familiar the AEDs (Table 1) and its side effects and should monitor the child on a regular basis [2].

Table 1: Antiepileptic drugs and pediatric dosing information.

Drug	Specific epilepsy indications	Dose [mg/kg body weight/ day]	Side effects
Carbamazepine	Focal, GTC and mixed types of seizures.	10–30 [in 2 divided doses]	Ataxia, diplopia, rash, hyponatremia, weight gain, tics. Exacerbates myoclonic and absence seizure.
Clobazam	Lennox-Gastaut syndrome (age >2 yr)	10-20	Slurred speech, loss of balance; appetite changes, drooling; sleep problems (insomnia).
Clonazepam	Absence, myoclonic seizures	0.05-0.2	Nuisance: dose-related neurotoxicity.
Ethosuximide	Absence epilepsy	20-30 [in 2 divided doses]	Abdominal discomfort, hiccups, headaches, sedation
Felbamate	Lennox -Gastaut Syndrome (>2 yr) Focal seizures (>14 yr)	30-60 [in 2 divided doses]	Insomnia, dizziness, headache, diplopia, aplastic anemia, hepatic failure, weight loss
Gabapentin	Monotherapy in focal seizures with and without secondary generalization	30-60 [in 3 divided doses]	Somnolence, dizziness, ataxia, weight gain, fatigue, blurred vision, diplopia, rash, aggressive behavior
Lamotrigine	Monotherapy in focal seizures, primary and secondarily GTC seizures, adjunctive therapy for Lennox–Gastaut syndrome	0.2–15 [in 2 divided doses] Slow titration	Skin rash, dizziness, ataxia, Stevens- Johnson syndrome, Precipitates myoclonic seizures. Stop drug if rash occurs
Levetiracetam	Myoclonic, partial and GTC seizures (age > 4-6 yr)	10 increase weekly to 15-45 in 2 doses	Sedation, behavioral symptoms are common
Methsuximide	Absence epilepsy	10–30 [in 2 divided doses]	Weight loss, hiccups, headache, dizziness, confusion
Oxcarbazepine	Monotherapy or adjunctive therapy for focal seizures (age >2 yr)	20-40 [in 2 divided doses]	Sedation, headache, ataxia, , apathy, rash, hypertrichosis gingival hypertrophy, hyponatremia
Perampanel	Partial seizures (>12 yr)	2-12	nausea, weight gain, vertigo, ataxia, gait disturbance
Phenobarbital	Focal seizures and GTC seizures	<5 yr, 3-5 >5 yr, 2-3	Sedation, drowsiness, hyperactivity, irritability, dysarthria, cognitive impairment

Phenytoin	GTC and focal seizures and status	< 3 yr, 8-10 >3 yr, 4-7 [in 2 divided doses]	Poor seizure control, fluctuating drug level, gum hyperplasia, hirsutism. Exacerbates myoclonic and absence seizure
Rufinamide	Lennox-Gastaut syndrome (age >4 yr)	30-45	Contraindicated in familial short QT interval
Tiagabine	Adjunctive therapy for focal seizures	15-45 [in 2 divided doses]	Sedation, dizziness, depression, nausea, vomiting, diarrhea, bruising
Topiramate	Monotherapy with new diagnosed epilepsy, GTC seizures, Lennox-Gastaut syndrome	Initial dose 0.5-1 Maintenance dose 5-9	Anorexia, weight loss, behavior, changes, hyperthermia, renal stones, acidosis
Valproic acid	Wide spectrum of action (age >2 yr)	15-60 [in 2-3 divided doses]	Nausea, weight gain, alopecia, hepatotoxicity, hyperammonemia, tremor, pancreatic toxicity
Vigabatrin	Monotherapy in treatment of infantile spasms, combination treatment for resistant focal epilepsy	150-200 daily or twice daily	Visual field defects [irreversible], ataxia, dizziness, diplopia, nystagmus, sedation, cognitive and behavioral disturbance, paraesthesia

Routine serum monitoring of anticonvulsant levels is not recommended because the practice is not cost effective. The indications for AED monitoring, including: (*) at the beginning of AED therapy; (*) for noncompliant children and caregivers; (*) during status epilepticus; (*) during accelerated growth spurts; (*) for patients on polytherapy (*) for patients with intractable seizures or seizures that have changed in type; (*) for manifestations of drug toxicity; and (*) for children with hepatic or renal disease [2,4].

The selection of the first (or subsequent) AED is affected by a combination of patient specific and AED- specific factors. Patient-specific factors include the child's disease characteristics (e.g., seizure type, epilepsy type and epilepsy syndrome) along with their commodities, communications, age, gender and ability to swallow pills. AED-specific factors include the drug's effectiveness and/or efficacy for a specific seizure type or epilepsy syndrome, its pharmacokinetic characteristics, dose dependent adverse effects, idiosyncratic reactions, chronic toxicities, teratogenicity and carcinogenicity [3].

If complete seizure control is accomplished by AED, a minimum of 2 seizure-free years is an adequate and safe period of treatment for a patient with no risk factors. AED is required for longer duration in epileptic syndromes and if there are multiple risk factors for recurrence. Prominent risk factors include age greater than 12 years at onset, neurologic dysfunction, a history of prior neonatal seizures and numerous seizures before control is achieved [2-4].

In order to assess response to treatment, information on the baseline seizure frequency and intervals between initial seizures is crucial. Tracking response to seizures is important, either with paper diaries or with online seizure tracking tools [3]. When the decision is made to discontinue the drug, the weaning process should occur in 3-6 months, because abrupt withdrawal may cause status epilepticus. Most epilepsies remit; relapse is reported in 11-41%, particularly during the first 6 months-2 years after discontinuation of AED. Restart previous AED, most patients will remit again. The risk factors for relapses, including: Epilepsies with structural brain lesions, abnormal neurological signs and abnormal EEG [4,5].

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