

General Principles of Medical Management of Epilepsy in Children

Abstract:

The primary purpose of epilepsy treatment is seizure control and the treatment of epilepsy is principally prophylactic. Although complete seizure control is the most important predictor of an improved quality of life, antiepileptic drugs (AEDs) can generate severe side effects, and the risk-benefit ratio must be considered before initiation of treatment. Correct recognition and differentiation between epileptic and non-epileptic paroxysmal events, and a diagnosis of the seizure type and syndromic form is necessary before starting the treatment. The initiation of AED treatment is usually recommended after 2 seizures, and being seizure-free for at least 2 years is necessary for treatment withdrawal. Therapy should be started using a single drug with a low-maintenance dose along with further upward titration. Overall, the first AED is finally successful in controlling the seizures in 50-70% of the cases. There is a consensus that being seizure free for 2 years is the most logical approach before stopping the AED treatment. Overall, about 50 % of the children with epilepsy will outgrow their epilepsy. Our goal in writing this article is to provide a systematic method of treatment and management of epilepsy in children.

Key words: epilepsy, quality of life, antiepileptic drugs

Introduction

The medical management of epilepsy is an art rather than the science of clinical pharmacology of antiepileptic drugs. Many factors must be considered for logical management. The first decision is to specify whether treatment is indicated considering the risk–benefit ratio in each patient, certainly age, gender, seizure type and general condition of the patient must be considered. (1).

A meticulous diagnostic assessment is required in this process because the type of treatment, its duration, and long-term prognosis are dependent upon an accurate exploration of seizure types and, if possible, the underlying epilepsy syndrome and relevant etiological factors (2). Our main purpose is to provide a systematic method of treatment and management of epilepsy in children.

Literature review

In general, the primary purpose of treatment should be seizure control, and the treatment of epilepsy is principally prophylactic. Antiepileptic drugs can generate severe side effects, and the patient should never suffer from the side effects of the treatment more than the symptoms of the disease. There is also a different definition for health related quality of life between the patients and their parents (3).

The treatment of epilepsy has a number of specific goals, and a balance needs to be drawn between the hazards of epilepsy and the hazards and benefits of therapy, that should be tailored to the requirements of the individual patient (4).

The benefits of drug treatment include recurrence prevention, avoidance of social consequences of epilepsy and secondary disability, suppression of subclinical epileptic activity, prevention of Epileptogenesis, improvement of quality of life, and reduction of mortality and morbidity.

Antiepileptic drugs are effective in control of the seizures in 80 to 90% of the patients and after 1-2 year seizure free period, long-term remission is seen in about 70% of all patients (4, 5).

Social and behavioral consequences of epilepsy can be more serious than seizure occurrence; for example, Deep Dark Secret Syndrome is a major concern. Seizure control results in the prevention of social consequences of epilepsy and secondary disabilities (6).

Antiepileptic drug therapy should be used to suppress seizures and not to reduce the EEG activity (7, 8). However, in some epileptic syndromes or epileptic encephalopathies, therapy can

be targeted at the suppression of electrical activity, including epileptic spasms, absence epilepsy, Landau–Kleffner syndrome and Lennox–Gastaut syndrome (9, 10). Suppression of electrical seizures in these conditions leads to improvement of cognitive functions.

Seizures may be induced in experimental animals through the phenomenon of kindling. In this model, repeated stimulation of the brain eventually leads to a generalized convulsion by changes in synapses; therefore, normal neurons can become epileptogenic by repeated stimulation (9, 11). The efficacy of AEDs in seizure control and improvement of the quality of life has been the topic of extensive studies and complete seizure control is the most important predictor of the improved quality of life (4, 12).

Epilepsy has some morbidity and mortality. For example higher rates of fractures and head injury, is seen in uncontrolled epileptic patients especially in generalized tonic clonic, atonic and myoclonic types. Epilepsy control may reduce the morbidity. Epilepsy is a potentially dangerous condition, a fact that is often overlooked (13). Antiepileptic drugs are able to decrease the mortality of epileptic patients. The main causes of death in relation to seizure are as follows: sudden unexpected death of epileptic patients (SUDEP) seizure- and epilepsy-related deaths, status epilepticus, death caused by accidents, and suicide. SUDEP is the most common seizure-related cause of death in epileptic patients that occurs after convulsive seizures (14). Patients at specific risk are those with a high frequency of convulsive seizures, symptomatic epilepsy, intellectual disability, and seizures during the sleep (15). SUDEP is usually the result of pulmonary derangement and cardiac arrhythmias (16).

The rate of SUDEP in different populations is mostly related to the frequency of tonic–clonic convulsions. Thus, in patients with largely controlled epilepsy, the risk seems to be about 1 death per 2500 patients per year, whereas the risk may be as high as 1–2 death per 100 patients per

year in patients with severe refractory epilepsy (17, 18). SUDEP is statistically very rare in children. SUDEP deaths are potentially preventable if the seizures are under control (19).

Status Epilepticus includes 1 to 2% of the deaths among epileptic patients, and it is relatively more common in children with intellectual disabilities. About 20% of the patients with convulsive status epilepticus admitted to the intensive care unit will not survive.

Death is usually due to the underlying cause, but skillful therapy will decrease the morbidity and mortality (20).

One study showed that the rate of suicide was extremely higher in epileptic patients than the general population and reported between 2 and 10% of causes of mortality in epilepsy. Drug overdose and psychiatric comorbidity of epileptic patients is usually the causes of suicide. Effective treatment of epilepsy will lower the risk of suicide (21, 22).

The side-effects of antiepileptic drugs can be generally classified as idiosyncratic reactions, dose-related reversible side effects, long-term irreversible side effects, and teratogenicity (23).

Idiosyncratic or hypersensitivity reactions are rare but life threatening conditions that results to bone marrow suppression and hepatic failure and anticonvulsant hypersensitivity syndrome with skin and other organs manifestations (24).

The risk of bone marrow or hepatic failure varies for different AEDs ; for example, for carbamazepine, the risk is 1 in 200,000 for aplastic anemia, 1 in 700,000 for agranulocytosis, and 1 in 450,000 for death associated with these events (25, 26). For felbamate, the risk is 1 in 2000 - 37,000 for aplastic anemia and 1 in 26,000- 34,000 for hepatotoxicity. For sodium valproate, the risk is 1 in 600 in children under 2 years of age with complex neurological disorders receiving polytherapy; in older patients the risk is 1 in 37,000 for monotherapy and 1 in 12,000 for polytherapy (24).

The drugs such as carbamazepine, phenytoin, phenobarbital, primidone and lamotrigine can cause acute hypersensitivity, a potentially harmful reaction that occurs in 1 in 1000 to 10,000 exposures. The primary manifestations include rash, fever, and lymphadenopathy accompanied by multi-organ system damage. The risk is highest (1 in 50 to 1 in 300) with lamotrigine in pediatrics, particularly when a high starting dose is consumed or when it is co-prescribed with sodium valproate. The frequency of Stevens–Johnson syndrome for carbamazepine is about 14 cases per 100,000. There is remarkable cross reactivity among these drugs at least for skin reactions, and it is better to avoid prescription of AEDs with probable cross reaction. Sodium valproate and benzodiazepines are safe drugs in this condition. Topiramate, gabapentin, levetiracetam, vigabatrin, pregabalin, and tiagabine have a low risk of hypersensitivity reactions (27). Early diagnosis and stopping of the drug improve the outcome of hypersensitivity reactions. Coarsening of feature due to chronic phenytoin consumption and visual field defects of vigabatrin are long-term nonfatal irreversible side effects. (9)

The most common adverse effects in patients treated for a long time are related to the central nervous system and include dysarthria, ataxia, dizziness, tremor, blurred vision, drowsiness, nystagmus, diplopia, fatigue, impairment of cognitive function, and disorders of mood and behavior. Chronic non-CNS adverse effects include weight gain with sodium valproate and vigabatrin, nephrolithiasis with topiramate, and endocrine disturbances with a variety of AEDs (9).

Correct recognition and differentiation between epileptic and non-epileptic paroxysms before the start of treatment is necessary.

In addition, every effort should be made to identify conceivable seizures and syndromic forms as soon as possible, because these are important in selection of drug and the prognosis of treatment (1, 5).

Drug therapy is usually recommended after occurrence of a second seizure. Treatment after a first seizure, however, may be considered with the presence of factors of high risk recurrence of seizures such as interictal epileptiform discharges or structural brain abnormalities. Status epilepticus in the first seizure episode and physical and psychological sequels of seizure recurrence are other conditions that must be considered for drug therapy after first unprovoked seizure. (5, 8, 28).

Patients with recurrent seizures usually require prophylactic antiepileptic drug therapy. In patients with brief seizures, occurrence only during the sleep without interference of daily activity therapy and some benign childhood epilepsies, therapy may be deferred even after recurrent seizures. (29, 30)

The prescription of an AED does not warranty seizure freedom (9).

Baseline hematological and biochemical investigations should be performed before drug initiation. Therapy should be started using a single drug. Initial titration should be to low-maintenance doses further upward titration will depend on the response and adverse effects (31). The advantages of monotherapy include better tolerance, better compliance, no adverse drug interaction, and cost effectiveness (32).

Some patients can be optimally controlled at low maintenance doses. With most AEDs, tolerance to CNS side effects occurs slowly after the start of treatment and immediate administration of a full maintenance dose may cause major tolerability problems. Drugs with most likely probability

of CNS side effects are primidone, topiramate, vigabatrin, benzodiazepines, and zonisamide. Even in idiosyncratic reactions the level of starting dose and the rate of dose increment may increase these potentially life threatening conditions especially with carbamazepine, phenytoin, and lamotrigine (32, 33).

A drug half-life is the time needed for the drug peak concentration in the blood to drop by 50%. According to pharmacokinetic principles, about five half-lives are needed to reach steady plasma concentrations after stabilizing the patient on a given dosage (33).

After prescription of one AED, 50-70% of the patients will be seizure free successfully. At least about five half-lives time is needed until one drug to reach a steady plasma concentrations. (33). About 40% of children will become seizure free with the first AED after some dose adjustment and step by step increasing of dosage to control seizures (32, 33).

If the first drug was not successful in seizure controlling, alternative monotherapies should be tried for 2- 3 times. Trials of combination therapy may be helpful in patients who failed two or more consecutive monotherapies. (1, 11, 34).

Evaluation of therapeutic response needs physician observation and diary record of seizures, time of seizure occurrence, precipitating factors of seizures and any side effects by patients or their parents. (3, 28).

Routine hematologic and biochemistic tests should be obtained before starting the treatment, and during treatment period. Parent's education for identifying and report of important side effects is main part of therapy especially , bleeding, bruising, fever , skin rash marked sedation, and vomiting . (35).

First follow-up visit is suitable after 4 to 6 weeks after starting the treatment and then every 3-6 months. Most AEDs can be successfully administered at twice per day and insisting that the drug must be administered exactly 12 hours apart is not evidence based. (1, 3, 7).

There is no doubt that the practice of monitoring the plasma drug concentration has improved the quality of epilepsy care. Feedback from the blood level measurement improves the clinician's experience and clinical acuity. There is a widespread opinion that the regular measurement of AED levels has a useful effect on compliance, drug toxicity, and seizure control (1, 36).

Inadequate therapeutic response, identification of the cause of side effects where these might be drug induced, pregnancy, liver disease, renal failure, gastrointestinal disease, hypoalbuminemic states, multiple drug therapy, and poor compliance are the situations in which blood level measurements are indicated (37).

Efficacy should not be determined by evaluation of changes in the EEG; however, EEG recordings may be helpful or even needed to evaluate the drug response in special conditions, e.g. in patients with absence epilepsy or epileptic encephalopathies and during treatment of status epilepticus (9, 38).

The decision on when to discontinue antiepileptic drugs is often difficult. The decision should be based on estimation of the risk of seizure recurrence. This risk is influenced by risk factors of seizure recurrence after drug withdrawal (11).

After 2-5 year period of successful treatment, risk of relapse after drug withdrawal is under 10%. In the end of at least 2 years seizure-free period counseling with patient and the family recommended for tapering of AED and concern of seizure recurrence (36).

Factors that increase the risk of seizure relapse are a short duration of therapy, long duration of active epilepsy, age above 16 years, certain types of seizure or epilepsy syndromes such as myoclonic seizures or juvenile myoclonic epilepsy and multiple seizure types. Other factors are multiple drug therapy, abnormal EEG, intellectual disability and abnormal neurological findings (39).

There is a general consensus that abrupt cessation of AEDs is unwise in the outpatient or inpatient setting, because it may not only increase the risk of seizure relapse but also accelerate prolonged seizures. Fifty percent of seizure recurrences occur during the reduction period and 25% in the first 6 months after AED withdrawal. In general terms, the slower the withdrawal, the less likely are the seizures to recur. Pediatric epileptologists generally recommend a withdrawal period of several weeks to several months. In patients on multiple AEDs, it is generally recommended that the drugs be withdrawn consecutively (11).

After assessing the risks and benefits, discontinuation begins if the patient is seizure free on AED for 2-5 years, has primary GTCS, has a normal neurologic examination, has a normal IQ, and has a normal EEG with treatment.

After AED withdrawal, in about 50% of the children epilepsy will be resolved. If first taper off of AED fails, about 60% will again become seizure free, and a second attempt to stop the medication will be successful in 60-70% of these children (40).

Conclusion

Medical treatment are the main standard therapy for epilepsy. Selection of an appropriate drug depends on proper recognition of the type of epilepsy or the epilepsy syndrome. For most

patients, the advantages of AEDs and seizure control outweigh the disadvantages. The main goals of AED therapy are prevention of seizure recurrences with minimal side effects.

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