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General Principles of the Medical Management of Epilepsy in Children: A Literature Review

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ABSTRACT

The primary aim of epilepsy treatment is seizure control, and the treatment is principally prophylactic. Although complete seizure control is the most important predictor of improved quality of life, antiepileptic drugs (AEDs) could cause severe side effects in the patients. Therefore, the risk-benefit ratio must be considered before the initiation of AED treatment. Accurate recognition and differentiation of epileptic and non-epileptic paroxysmal events and the diagnosis of the seizure type and epilepsy syndrome are essential procedures before AED treatment. It is often recommended that AED treatment start after two seizures, and being seizure-free for a minimum of two years is a prerequisite for treatment withdrawal. The AED treatment process must be initiated with a single drug at a low maintenance dose, along with further upward titration. Overall, the first attempt in AED treatment has been reported to effectively control seizures in 50-70% of the cases. Moreover, there is a consensus that being seizure-free for two years is the most valid approach to discontinue AED treatment. Approximately 50% of the children with epilepsy outgrow their disease. The present study aimed to provide a systematic method for the treatment and management of epilepsy in children.

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Introduction

Medical management of epilepsy is an art rather than a science of the clinical pharmacology of antiepileptic drugs. Several factors must be considered for the effective management of epilepsy. The first decision in this regard is to specify the treatment indications based on the risk-benefit ratio in each patient. Other factors to be taken into account are age, gender, seizure type, and general condition of the patient (1).

Epilepsy management requires a meticulous diagnostic assessment since the type of treatment, its duration, and long-term prognosis depend on the accurate examination of the seizure type, as well as the underlying epilepsy syndrome and relevant etiological factors (2).

The present study aimed to provide a systematic method for the treatment and management of epilepsy in children.

Literature Review

In general, the primary aim of epilepsy treatment is seizure control, and the treatment is principally prophylactic. However, antiepileptic drugs could cause severe side effects, and the patients

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should never suffer more from the complications of the treatment than the symptoms of the disease. Of note, there are diverse conceptions toward health-related quality of life in young patients and their parents (3).

Epilepsy treatment has specific goals, and a balance must be drawn between the hazards of epilepsy and the risks and benefits of epilepsy treatment in accordance with the individual needs of patients (4). The benefits of drug treatment in epileptic patients include the prevention of seizure recurrence, avoidance of the social consequences of epilepsy and secondary disabilities, suppression of subclinical epileptic activities, prevention of epileptogenesis, improved quality of life, and reduced mortality and morbidity.

Antiepileptic drugs (AEDs) have proven effective in controlling seizures in 80-90% of the patients. After 1-2 years of AED treatment, reports have suggested a seizure-free period, and long-term remission in approximately 70% of patients (4,5).

Social and behavioral consequences of epilepsy might be more threatening than seizure occurrence; one of the major concerns in this regard is the deep dark secret syndrome. Seizure control has been shown to prevent the social consequences of epilepsy, as well as the associated secondary disabilities (6).

AED therapy should be used to suppress seizures and not to reduce electroencephalography (EEG) activity (7,8). However, in some epileptic syndromes or epileptic encephalopathies, therapy could be targeted at the suppression of electrical activity, such as epileptic spasms, absence seizures, Landau-Kleffner syndrome, and Lennox–Gastaut syndrome (9,10). Suppression of electrical seizures under such circumstances leads to the improvement of cognitive functions.

Seizures could be induced in experimental animals through the kindling phenomenon. In this model, repeated brain stimulation eventually leads to a generalized convulsion by changing the synapses; therefore, normal neurons may become epileptogenic due to repeated stimulation (9,11).

Extensive research has focused on the effectiveness of AEDs in seizure control and improvement of the quality of life. Complete seizure control is considered to be the most important predictor of improved quality of life in epileptic patients (4,12).

Epilepsy is associated with morbidity and mortality, such as the higher incidence of fractures and head injuries, which is often observed in uncontrolled epileptic patients, especially in those with generalized tonic-clonic, atonic, and myoclonic seizure types. Epilepsy control could reduce the morbidity of the disease.

Epilepsy is a potentially hazardous condition, which is commonly overlooked by specialists and physicians (13). AEDs decrease the mortality rate in epileptic patients. Some of the main causes of mortality due to epileptic seizures include sudden unexpected death in epilepsy (SUDEP), epilepsy-related deaths, status epilepticus, death due to accidents, and suicide. SUDEP is the most common seizure-related cause of mortality in epileptic patients, which occurs after convulsive seizures (14). Specifically high-risk epileptic patients in this regard are those with a high frequency of convulsive seizures, symptomatic epilepsy, intellectual disability, and seizures during sleep (15).

SUDEP might also be the result of pulmonary derangement and cardiac arrhythmias (16). The rate of SUDEP in different populations is correlated with the frequency of tonic-clonic convulsions. As such, the risk of SUDEP in the patients with adequately controlled epilepsy has been estimated to cause one death per 2,500 patients per year, whereas the risk may be as high as 1-2 deaths per 100 patients per year in with the cases with severe refractory epilepsy (17,18). Statistically, SUDEP is quite rare in children. The mortality associated with SUDEP is potentially preventable if the seizures are effectively controlled (19).

Status epilepticus accounts for 1-2% mortality in epileptic patients and is relatively more common in children with intellectual disabilities. Approximately 20% of the patients with convulsive status epilepticus admitted to intensive care units cannot survive.

In epilepsy, mortality is often due to underlying causes, and effective therapy has been shown to decrease mortality and morbidity in the patients (20). Findings of a study in this regard indicated that the rate of suicide was extremely higher in epileptic patients compared to the general population, accounting for 2-10% mortality in epilepsy. Drug overdose and psychiatric comorbidities are among the common causes of suicide in epileptic patients. Effective treatment of epilepsy could significantly lower the risk of suicide (21,22).

The side-effects of AEDs are classified as idiosyncratic reactions, dose-related reversible side-effects, long-term irreversible side-effects, and teratogenicity (23). Hypersensitivity or idiosyncratic reactions are rare, life-threatening conditions that lead to bone marrow suppression, hepatic failure, and anticonvulsant hypersensitivity syndrome with manifestations in the skin and other organs (24).

The risk of bone marrow suppression or hepatic failure varies depending on the type of AEDs. For instance, the risk associated with carbamazepine has been estimated at one per 200,000 in aplastic

anemia, one per 700,000 in agranulocytosis, and one per 450,000 in the mortalities associated with these conditions (25,26). As for felbamate, the risk has been estimated at one per 2,000-37,000 in aplastic anemia and one per 26,000-34,000 in hepatotoxicity. Use of sodium valproate is associated with the risk of one per 600 in the children aged less than two years with complex neurological disorders receiving polytherapy. In older patients, the risk is one per 37,000 in monotherapy and one per 12,000 in polytherapy (24).

Other AEDs (e.g., carbamazepine, phenytoin, phenobarbital, primidone, and lamotrigine) may cause acute hypersensitivity, which is a potentially detrimental reaction that occurs in one per 1,000-10,000 exposures. The primary manifestations include rashes, fever, and lymphadenopathy, accompanied by multiple organ system failure. The risk is considered to be highest (one per 50 to one per 300) with lamotrigine in pediatric care, particularly with a high initiation dose or co-prescription with sodium valproate. In addition, the frequency of Stevens-Johnson syndrome with the use of carbamazepine has been estimated at 14 cases per 100,000.

There is remarkable cross-reactivity among AEDs at least in the case of skin reactions. Therefore, it is often recommended that the prescription of AEDs with possible cross-reaction be avoided. Sodium valproate and benzodiazepines are considered to be safe in this regard. On the other hand, AEDs such as topiramate, gabapentin, levetiracetam, vigabatrin, pregabalin, and tiagabine are associated with a low risk of hypersensitivity reactions (27). Early diagnosis and discontinuation of AED treatment could improve the outcome of hypersensitivity reactions. Some of the long-term, nonfatal, irreversible side-effects of AEDs include the deterioration of the symptoms due to chronic phenytoin consumption and visual field defects due to the overuse of vigabatrin (9).

In the epileptic patients receiving long-term AED treatment, the most common adverse effects of the drugs affect their central nervous system (CNS), manifesting as dysarthria, ataxia, dizziness, tremor, blurred vision, drowsiness, nystagmus, diplopia, fatigue, impairment of cognitive function, and mood and behavioral disorders. Chronic non-CNS adverse effects include weight gain with sodium valproate and vigabatrin, nephrolithiasis with topiramate, and endocrine disturbances with multiple AEDs (9).

Accurate recognition and differentiation of epileptic and non-epileptic paroxysms is essential before initiating AED treatment. In addition, conceivable seizures and epilepsy syndromes must be identified as soon as possible for the proper selection of drugs and treatment prognosis (1,5).

AED therapy is usually recommended after the occurrence of a second seizure. However, initiating AED treatment after the first seizure might be considered in the presence of the predisposing factors for the recurrence of seizures, such as interictal epileptiform discharges or structural brain abnormalities. Status epilepticus in the first seizure and the physical and psychological sequels of seizure recurrence are among the other conditions to be considered for AED therapy after the first unprovoked seizure (5,8,28).

Patients with recurrent seizures often require prophylactic antiepileptic drug therapy. In the patients with brief seizures and episodes only during sleep without interference in daily activities, as well as in some benign childhood epilepsies, AED therapy could be deferred even after recurrent seizures (29,30). It is notable that the prescription of an AED does not warranty seizure freedom (9).

Baseline hematological and biochemical investigations should be performed before AED initiation. Furthermore, AED therapy should begin with a single drug, and the initial titration should be at low maintenance doses, followed by further upward titration depending on the patient's response and treatment complications (31). In this regard, the advantages of monotherapy include better tolerance, better compliance, no adverse drug interaction, and cost-effectiveness (32).

Some epileptic patients could be optimally controlled at low maintenance doses of AEDs. With most AEDs, tolerance of the CNS-related side-effects occurs slowly after initiating treatment, and the immediate administration of a full maintenance dose may cause major tolerability problems. AEDs with the highest risk of CNS side-effects are primidone, topiramate, vigabatrin, benzodiazepines, and zonisamide. Even in idiosyncratic reactions, the starting dose and dose rate increment may increase the risk of potentially life-threatening conditions, especially with carbamazepine, phenytoin, and lamotrigine (32,33).

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

After the prescription of one AED, 50-70% of the patients have been reported to be seizure-free. Moreover, approximately 40% of epileptic children become seizure-free with the first AED after some dose adjustment and gradual increasing of the drug dosage to control seizures (32,33). If the first drug is not effective in seizure control, alter-

native monotherapies should be attempted 2-3 times. In addition, trials of combination therapy may be helpful in the patients who failed two or more consecutive monotherapies. (1,11,34). Evaluation of the therapeutic response requires physician observation and recording of the seizures, time of seizure occurrence, precipitating factors of seizures, and drug side-effects by the patients or their parents (3,28).

Routine hematology and biochemistry tests should be carried out before starting the treatment, as well as during the treatment period. Parental training on identifying and reporting of important side-effects plays a key role in AED therapy, especially in the case of bleeding, bruising, fever, skin rashes, marked sedation, and vomiting in the patient (35). The first follow-up visit should be performed 4-6 weeks after initiating treatment, repeating every 3-6 months afterwards. Most AEDs could be successfully administrated twice per day, and the claim that drugs must be administered at precise 12-hour intervals is not evidence-based (1,3,7).

Undoubtedly, monitoring of the plasma drug concentration could improve the quality of epilepsy care. Moreover, providing feedback on the blood level measurement could increase the experience of clinicians, while enhancing clinical acuity. A common notion in this regard dictates that the regular measurement of AED levels positively influences patient compliance, drug toxicity, and seizure control (1,36). Blood level measurements are indicated in various conditions, including inadequate therapeutic response, identification of the cause of drug-induced side-effects, pregnancy, liver disease, renal failure, gastrointestinal disease, hypoalbuminemia, multiple drug therapy, and poor compliance (37).

The effectiveness of AED treatment should not be determined by evaluating the changes in the EEG. However, EEG recordings may be helpful or even needed to evaluate the drug response under particular circumstances; such examples are the patients with absence epilepsy or epileptic encephalopathies and during the treatment of status epilepticus (9,38).

The decision about the time of discontinuing AEDs is often difficult and should be based on the estimated risk of seizure recurrence, which is affected by the risk factors of seizure recurrence after drug withdrawal (11). After 2-5 years of successful treatment, the risk of relapse after drug withdrawal decreases to less than 10%. By the end of a minimum of two years of seizure-free period, counseling for patients and their families is recommended for the tapering of AEDs and address the concerns about seizure recurrence (36).

The risk of seizure relapse increases due to the short duration of therapy, long duration of active epilepsy, age of more than 16 years, certain seizure types or epilepsy syndromes (e.g., myoclonic seizures or juvenile myoclonic epilepsy), and multiple seizure types. Other predisposing factors in this regard are multiple drug therapy, abnormal EEG, intellectual disability, and abnormal neurological findings (39).

There is a general consensus that the abrupt cessation of AEDs is reckless in outpatient or inpatient settings since it may not only increase the risk of seizure relapse, but also accelerate prolonged seizures. According to statistics, 50% of seizure recurrences are reported during the AED reduction period, and 25% occur within the first six months after AED withdrawal. In general, gradual withdrawal lowers the risk of seizure recurrence. Pediatric epileptologists normally recommend a withdrawal period of several weeks to several months. In the patients receiving multiple AEDs, it is generally recommended that the drugs be withdrawn consecutively (11).

After assessing the risks and benefits, discontinuation of AEDs begins if the patient is seizure-free on AED for 2-5 years and has primary generalized tonic-clonic seizures, normal neurological examination, normal IQ,, and normal EEG with treatment. After AED withdrawal, epilepsy is resolved in approximately 50% of children. With the failure of the first taper off of AED, about 60% of patients become seizure-free again, and a second attempt to discontinue the medication has been reported to be successful in 60-70% of epileptic children (40).

Conclusion

Medical treatment is the main standard therapy for epilepsy. Selection of an appropriate drug depends on the proper recognition of the type of epilepsy or epilepsy syndromes. In the majority of epileptic patients, the advantages of AEDs and seizure control outweigh the disadvantages. The main goal of AED therapy is the prevention of seizure recurrence with minimal side-effects.

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Conflict of Interest

The authors declare no conflict of interest.

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