TREATMENT OF REFRACTORY EPILEPSY*

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ABSTRACT

Despite advances in pharmacotherapy, refractory epilepsy continues to be a significant problem for many pediatric patients. No uniform definition of intractable epilepsy exists. When true pharmacoresistance is present, the ketogenic diet, vagus nerve stimulation, and seizure surgery are alternative therapeutic options. Clinical considerations of various treatment modalities in refractory childhood epilepsy are discussed in this article. (Adv Stud Med. 2005;5(5B):S470-S473)

Approximately 80,000 new cases of epilepsy are diagnosed each year in children. Fortunately, many of these young patients achieve spontaneous remission; but for those patients who do not, the consequences of intractability can be quite severe, including status epilepticus, cognitive decline, lowered socioeconomic potential, and profound stress on the entire family. Children and their families may encounter significant problems in academic and social achievement and personal and family lifestyle plus financial pressures caused by prolonged medical treatment. Children with intractable seizures may also sustain significant injuries caused by falls and other accidents.

The primary goal of epilepsy therapy is the absence of seizures without treatment adverse effects. Some antiepileptic drugs (AEDs), such as phenobarbital, offer excellent antiseizure efficacy but have intolerable adverse effects. Physicians caring for developing children must be acutely aware of the safety implications of these agents with regard to brain development, bone health, and other issues—short term and long term. AEDs can interact significantly with other drugs, as in the case of their well-known potential for interaction with birth control pills in our adolescent patients.

WHAT IS REFRACTORY EPILEPSY?

Existing medical literature shows that 10% to 30% of newly treated patients with epilepsy do not respond to medication, despite adequate treatment with appropriate AEDs. This article describes characteristics of adequate antiseizure therapy, explores common reasons for failure of AED treatment, and offers selected caveats regarding monotherapy and combination therapy with antiepileptic agents. Nonmedical treatment options and common causes of drug resistance in patients with epilepsy are also discussed.

A recent study involving 525 children and adults demonstrated seizure resolution in approximately 50% of all patients following treatment with a single AED.1 These patients’ chance of attaining remission dropped precipitously as further antiseizure agents were used unsuccessfully, as only 4% of the patients became seizure-free after 3 AEDs were used, alone or in combination. Overall, 33% of all patients in this study eventually were found to have intractable epilepsy.

In a recent prospective study, 10% of 613 children had intractable epilepsy, defined as the failure of 2 or more AEDs over an 18-month period.2 An earlier longitudinal study involving 417 children with partial and generalized tonic-clonic seizures indicated remis-
sion in 80% of patients who were able to remain on a single AED for 1 year. In this group, 17% of the children (typically those patients with underlying neurologic deficits) required treatment with additional AEDs. Overall, 25% of the children in this study who did not respond to one AED had refractory epilepsy.

A recent international review involving 7 independent studies of childhood epilepsy found that long-term remission occurs in approximately 60% of children overall. Factors favoring remission include the absence of significant neurologic and intellectual deficits, age younger than 12 years at seizure onset, and the presence of infrequent, easily controlled seizures. The presence of all these factors was associated with a remission rate of 80%; the remission rate fell to 20% when these factors were absent.

**Epilepsy Treatments**

**Antiepileptic Drugs**

Since 1993, 9 new AEDs have been introduced in the United States. As compared with the older drugs, some of these drugs involve fewer adverse effects and are easier to use, as blood levels are not determined as often. Mechanisms of AED action are summarized in Table 1.

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<thead>
<tr>
<th>Na⁺ Channels</th>
<th>Ca²⁺ Channels</th>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>Ethosuximide</td>
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<tr>
<td>Lamotrigine</td>
<td>Topiramate</td>
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<tr>
<td>Oxcarbazepine</td>
<td>Zonisamide</td>
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<td>Phenytoin</td>
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<th>Inhibitory Transmission</th>
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<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Felbamate</td>
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<td>Gabapentin</td>
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<td>Phenobarbital</td>
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Ca²⁺ = calcium; Na⁺ = sodium. Data from Kwan et al.

**Common Causes of Antiepileptic Drug Failure**

Antiepileptic drug therapy may be ineffective for many reasons. Correct diagnosis may be difficult at times because physicians must often rely on second-party and third-party observation of seizure events. The diagnostic picture may be complicated by pseudoseizures and other factors and by comorbidities, such as autism, spastic cerebral palsy, and repetitive tic movements. Therefore, a video electroencephalogram (EEG) may be used in many cases to identify exactly what is happening with the patient.

Patients may be treated with a correct AED but are given an inadequate dose or a too short a trial of the medication, as patients with difficult-to-control seizures often require AED doses near the maximum limit of tolerability. Some newer agents are used successfully at much higher than recommended doses but obviously with careful attention paid to adverse-effect outcomes. Physicians must understand that it is sometimes more effective to push a single AED to maximum tolerated levels than to add a second medication in patients who have experienced 1 seizure on an initial AED. Failure to use the recognized drug of choice for specific seizure syndromes can, of course, affect treatment effectiveness.

Promoting treatment compliance is an important part of treating childhood epilepsy and often comprises a major issue in treatment effectiveness. If parents or caregivers are not compliant with therapy, the causes of this noncompliance must be carefully, and often delicately, explored. AED noncompliance may be because of family members’ fears about a drug’s long-term adverse effects or the high cost of these agents, which may not be covered by third-party payers. Furthermore, denial may play a part when caregivers express concerns about the effectiveness of or the need for specific AEDs. Pill boxes and seizure calendars can help families improve treatment compliance, and sometimes drug levels must be
monitored and office-visit frequency increased when more physician supervision is necessary.

Radiologic data should be re-evaluated carefully to rule out structural causes for AED ineffectiveness. Very high-quality, high-resolution magnetic resonance imaging studies are necessary, and any questionable studies should be repeated. Also, healthcare providers must be aware that orthodontic braces can cause artifactual findings in radiologic studies done in children, thus these braces must sometimes be temporarily removed and the original studies repeated to confirm that nothing has been missed or misinterpreted.

Physicians are aware that certain seizure syndromes may be inherited within families, and recent excellent work in pharmacogenomics has made it clear that drug resistance can also be associated with certain genotypes. Future work in this area may lead to genetic tests that are of practical use in identifying patients who are genetically resistant to certain AEDs.

**Antiepileptic Drug Treatment Strategies**

In selecting single and multiple treatment agents, physicians must carefully consider the potential effect of comorbidities, such as mood instability, headaches, and other factors, that commonly accompany childhood epilepsy. AED monotherapy offers clear advantages, especially in children, with regard to fewer adverse effects and drug-to-drug interactions, better patient compliance, and lower cost. However, when an initial AED proves ineffective, an appropriate second agent can be added and the initial drug withdrawn after an evaluation has been made of the effect of the 2 drugs together. It is essential during this process to carefully obtain feedback from the family about the drug's effect on the child's seizures and to note any adverse effects or problems when each agent is administered alone and when both agents are administered together. Table 2 summarizes AED combinations that may be helpful in refractory forms of epilepsy.6-9

Studies have shown that ethosuximide and valproate are effective in treating absence seizures.6 Lamotrigine must be used carefully in combination with valproate in treatment of combination partial and generalized seizures because of the increases in drug half-life, although this effect may at times be advantageous.7,8 Lamotrigine plus topiramate is effective for combination partial and generalized seizures and in the treatment of partial seizures alone.9

**Predicting Drug Resistance**

Approximately 10% to 30% of children with epilepsy exhibit some degree of resistance to AEDs, defined as the failure of 2 or more agents. In one study, AED resistance was associated with high initial seizure frequency, syndromic groupings, and significant focal slowing on EEG.2 Another investigation identified early myoclonic encephalopathy, early infantile epileptic encephalopathy, severe myoclonic epilepsy in infancy, and the presence of Lennox-Gastaut syndrome or infantile spasms as indicators associated with increased rates of AED resistance.10 High initial seizure frequency is associated with drug resistance, as are mixed seizure types, early seizure breakthrough, abnormal neurologic status, neonatal seizures, and the presence of status epilepticus and tumors or other underlying structural abnormalities.11

**Nonmedication Options**

**Ketogenic Diet**

The ketogenic diet, which was developed more than 80 years ago, controls seizure activity by a mechanism that has not yet been identified. The dietary changes involved are complicated and require extensive family commitment, but they may be extremely effective in seizure reduction.12 The diet includes 80% to 90% of calories from fat, protein appropriate for growth, and extreme carbohydrate restriction; the diet typically is more successful with younger children in whom diet is easily controlled by parents. Potential adverse effects of the ketogenic diet include lethargy, weight loss, nausea and vomiting, constipation, and diarrhea.

Table 2. Combination Therapy in Childhood Epilepsy

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<tr>
<th>Combination</th>
<th>Seizure Type</th>
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<tr>
<td>Ethosuximide + sodium valproate</td>
<td>Absence†</td>
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<tr>
<td>Lamotrigine + sodium valproate</td>
<td>Combine partial/generalized‡</td>
</tr>
<tr>
<td>Lamotrigine + topiramate</td>
<td>Combine partial/generalized;</td>
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<td>generalised‡</td>
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Data from Rowan et al; Pisani et al; Brodie and Yuen; and Stephen et al.
Furthermore, the diet’s use necessitates the frequent monitoring of complete blood count levels, electrolyte values, and liver and renal status, as additional infrequent adverse effects can include hyperlipidemia, hypoglycemia, hypocalcemia, electrolyte imbalances, and metabolic acidosis, in addition to cardiac and renal abnormalities. Families interested in this option should be advised to read Dr John Freeman’s book on epilepsy diet treatment to gain a clear idea of the commitment, responsibilities, and potential adverse effects involved in this approach. Less restrictive ketogenic diets, such as the modified Atkins diet, have also demonstrated promise regarding seizure reduction and are the subject of ongoing research.

Epilepsy Surgery

Surgery continues to be used as a treatment for refractory pediatric epilepsy. Appropriate surgical candidates have clearly demonstrated refractory epilepsy (a localized, potentially removable area of epileptogenic focus) and must be at low risk for new neurologic deficits caused by the surgery. Before pursuing any surgical approach to treatment, families must understand that surgical intervention is a long-term process requiring a consistent clinical history, positive radiologic and neuropsychologic evidence in support of surgical intervention, and favorable neuropsychologic findings. After this careful screening, success rates of surgical intervention can be significant, with remission rates of 60% to 80% after anterior temporal lobectomy, and as high as 70% after lesional extratemporal resection, hemispherectomy, and multilobar resection.

Conclusions

Physicians who care for children with refractory epilepsy, in addition to their families, cannot afford to be pessimistic. As the pioneering neurologist William Lennox, MD, observed in 1928, “One who is confronted with the task of controlling seizures in a person with epilepsy grasps at any straw.” Pediatric neurologists face difficult tasks every day in the treatment of refractory epilepsy and must make the best use of all available “straws,” including drug and diet therapy, vagus nerve stimulation, and surgical intervention, to help children with refractory epilepsy approach a better life.

References