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Antiepileptic drug trials with greater attention to daily clinical practice and special epilepsy syndromes

Wei-Ping LIAO

Institute of Neurosciences and the 2nd Affiliated Hospital of Guangzhou Medical College, Guangzhou, China

Abstract

Most of the present antiepileptic drug trials focus on efficacy and short-term safety with limited information relevant for daily clinical practice, such as spectrum of efficacy, effective dose, titration method, drug interactions, and long-term outcome. Antiepileptic drug trials more akin to daily clinical practice should also be emphasized in future trials. There are, limited randomized control trials for certain seizure types or epilepsy syndromes, such as Lennox-Gastaut syndrome and severe myoclonic epilepsy in infancy. The author proposed self-controlled "class S" study in patients who has well-defined epilepsy syndrome with homogeneity in evolution of illness and high frequency of seizures.

The clinical evaluation of the efficacy of antiepileptic drugs (AEDs) has been greatly improved due to the introduction of randomized controlled trials (RCTs). Most of the AEDs, especially new AEDs, have been evaluated using these methods in the past two decades. There is no doubt that standard RCT provide important evidence of efficacy of AEDs. However, the data from RCTs have limitations. Two aspects for special consideration for future AED trials are discussed in this paper.

ANTIEPILEPTIC DRUG TRIALS MORE AKIN TO DAILY CLINICAL PRACTICE

Most of the present AED trials focus on efficacy and short-term safety with limited information relevant for daily clinical practice, such as spectrum of efficacy, effective dose, titration method, drug interactions, and long-term outcome. Thus, AED trials more akin to daily clinical practice should also be emphasized. Furthermore, patients of different ethnicity may show differences in response. For example, lamotrigine and topiramate are now available in many Asian countries. There may be differences in responses to these AEDs among the Asians as compared to the West. In a group of 126 Chinese patients using lamotrigine, it was found that 89% of patients with 50% seizure reduction had lamotrigine serum concentration between 1-8μg/ml. The side effect was significantly higher in patients with lamotrigine concentration >8μg/ml. Skin rash could be avoided with lower initial dose and slower titration method.[1] The therapeutic range of lamotrigine was suggested to be 1-4 μg/ml in earlier report, and allergic reaction was found in 5-10% of patients in the data from the West. For Topiramate, in a Chinese study, the effective dose was usually <200mg/day (average 123.9±47.9mg/day) for adults, and <5mg/kg/day (3.6±1.2 mg/kg/day) for children. These doses were lower than that used in the West. Better seizure control was achieved in 18% of patients after decreasing the dosage from their maximally achieved dose. Anorexia was the most frequent adverse events, anhidrosis and low grade fever were common in children; all these were different from the data of the West.[2]

ANTIEPILEPTIC DRUG TRIALS FOR SPECIAL EPILEPSY SYNDROME

The evidence from a RCT is classified and rated according to the rating of the RCT. Evidence-based guideline has also been developed to assist clinicians with the treatment of epilepsy by The International League Against Epilepsy (ILAE). The methodology recommended in the ILAE treatment guidelines is expected to be widely used in future AEDs trials.[3] There are sufficient data for partial-onset seizures and less so for generalized-onset tonic-clonic seizures. This is particularly so for adults as compared to children. There are, however, only few or no RCTs for certain seizure types or epilepsy syndromes, such as Lennox-Gastaut syndrome and severe myoclonic epilepsy in infancy. The treatment of

Address correspondence to: Dr. WP Liao, Institute of Neurosciences and the 2nd Affiliated Hospital, Guangzhou Medical College, Guangzhou, 510260, China. Phone: +86-20-34152625, Fax: +86-20-34153378, Email: wpliao@tom.com

such epilepsy syndromes is still a challenge in clinical practice. In children, however, it is much more difficult to conduct a high level RCT with the methodology proposed in the ILAE treatment guideline, especially for epilepsy syndrome with frequent or refractory seizures. This is because there are usually less number of patients in a particular center. The high frequency of seizures also do not allow for a long-duration fixed dose regime. The placebo effect is probably less important in young children. A self-controlled, open-label study is more practical in this situation. It is reliable if the epilepsy syndrome meets the following criteria:

1. Well-defined epilepsy syndrome with characteristic seizure manifestations, precipitating factors, age of onset, severity, clinical course, anatomical site of involvement, prognosis, and etiology.
2. High frequency of seizure means that it may be easier to demonstrate the effect of an AED within a shorter observation period.
3. Additional characteristic variables for evaluation of efficacy, such as EEG. Although EEG is usually not used as a outcome variable in AED assessment, an objective and characteristic pattern such as 3Hz spike and wave do help in the evaluation of efficacy.
4. Homogeneity in evolution of the illness. Epilepsy syndromes such as Lennox-Gastaut syndrome show homogeneity in the clinical course without spontaneous remission. Treatment response can be observed when the AED is effective. On the other hand, for syndromes with fluctuating frequency of seizures and spontaneous remission, a self-controlled study is inappropriate.

For the epilepsy syndromes that have the above characteristics, a self-controlled study with the following criteria is suggested. The class of study suggested is "class S". Thus, class S study is a self-controlled study that meets the following criteria:

1. Primary outcome variable: efficacy or effectiveness
2. Treatment duration: 48 weeks and information on 24 weeks seizure freedom data (efficacy) or 48 weeks retention data (effectiveness); and sufficient duration that depends on the base-line seizure frequency for a treatment dose in open-label study
3. Study design: Self-controlled; randomized if using a proven effective comparator
4. Superiority demonstrated, or if no superiority demonstrated, the study's actual sample size was sufficient to show noninferiority of no worse than a 20% relative difference in effectiveness/efficacy
5. Appropriate statistical analysis

Evidence from a class S study is suggested to be termed "level S". This is a preliminary suggestion; more work is needed for further improvement.

ROLE OF GENOTYPES IN FUTURE DRUG TRIALS

Severe myoclonic epilepsy in infancy is a syndrome characterized by prolonged partial febrile seizures in the first year of life. It is followed by febrile or afebrile intractable epilepsy with both generalized and localized seizure types and mental handicap. Mutations in *SCN1A* gene have been identified in 30% to 90% of children. It has been reported that lamotrigine, an AED that mainly act on sodium channel, can induce seizure aggravation.[4] It has been shown that lamotrigine aggravate seizures in some severe myoclonic epilepsy patients but improve seizures in others.[5] Two mutations in *SCN1A* gene (c.2837G>A:R946H; c.5295T>A:F1765L), which is near the binding site of lamotrigine, were identified in patients with seizure aggravated by LTG.[6] R946H have been reported in patient with severe myoclonic epilepsy.[7] Although shown to be refractory to some AEDs, the two patients became seizure-free with valproate and topiramate.[6] Both these AEDs have multiple mechanism of action, indicating that the intractability of severe myoclonic epilepsy can be avoided if appropriate treatment is given. Genotype may be an important consideration in future drug trials, as well as in clinical practice.

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