Combination Therapy of Antiepileptic Drugs (AEDS) With Safe Natural Anticonvulsant Agent

Hakimeh Gavzandarounkola1 and Mohammad Sayyah2
1Department of Basic Sciences, Faculty of Veterinary Medicine, Amol University of Special Modern Technologies, Amol-Iran
2Department of Physiology and Pharmacology, Pasteur Institute of Iran, Tehran, Iran

Corresponding author: Hakimeh Gavzandarounkola, Department of Basic Sciences, Faculty of Veterinary Medicine, Amol University of Special Modern Technologies, Amol-Iran, Tel: +98 21 66963311-20; E-mail: h.gavzan@hotmail.com

Commentary

Epilepsy is the third most common neurological disorder after stroke and Alzheimer's disease. Treatment of epilepsy has advanced during the past three decades by several third generation antiepileptic drugs (AEDs). Yet, resistance to AEDs, as well as intolerability in 20% to 30% of the patients, generates demands for developing new drugs or strategies for treatment of epilepsy [1]. Furthermore, AEDs side effects and their toxicities are the other problem of drug treatment. Combination therapy is one of the most recommended strategies for treatment of refractory epilepsy. It is based on synergistic anticonvulsant action, an antagonistic action with respect to adverse effects, or both. Moreover, combination therapy could minimize side effects and toxicities of conventional AEDs by lowering of drug doses. Combination therapy of conventional AEDs with newer anticonvulsant agents could be useful because new mechanisms of synergism may be recognized.

There are several types of combination therapy in preclinical test. Isobolographic analysis and COMPUSYN software are two common methods. Isobolographic analysis compares the dose of each agent that produced anticonvulsant effect in 50% of animals (ED50) alone and in co-administration by log-probit analysis. In this method, animals tested by several fixed-ratio combinations e.g. 1:1, 1:3 and 3:1 were calculated from ED50 of each drug used alone. These fixed-ratio combinations are equivalent to additive doses theoretically calculated. Then these fixed-ratio combinations tested in animals and determined the experimental ED50 of fixed-ratio combinations. Significant lowering of experimental ED50 of fixed-ratio combinations than theoretical ED50 of them show synergistic effect. [2-4]. In COMPUSYN software method, degree of drug interaction was determined according to combination index (CI) method. CI is obtained from the following equation: CI= (Dx1 +Dx2) / D1 + D2 where D1 and D2 are the doses of two drugs used in mixture. (D1 + D2) ‘in combination' produces x% protection. (Dx1) and (Dx2) are D1 and D2 alone that shows x% protection. [5]. A CI value equal to 1 indicates additive interaction. A CI smaller than 1 denotes synergism, and a CI greater than 1 suggests antagonism. An isobologram plot was drawn by COMPUSYN software. The isobologram is a graph of equipotency doses for two drug combinations, which is simply created by setting the CI equation equal to 1 for EDx [6]. Co-administration strategy of the safe and inexpensive natural anticonvulsant compounds with AEDs could be favourably regarded in clinical studies of epilepsy treatment.

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) as one of the anticonvulsant natural agent have been proposed in recent years to treat epilepsy [7]. They are dietary lipids, which constitute 30% of brain

lips. Among the n-3 PUFAs, only DHA is the most abundant and the most bioactive fatty acid in the brain [7]. Numerous in vitro, in vivo, and clinical studies have evaluated possible anticonvulsant activity of DHA, with positive or negative results. According to the nonclinical studies, anticonvulsant potency of DHA is much lower than that of the current standard AEDs [7-14]. Interestingly, by Isobolographic analysis, our last study showed that DHA at ED25 caused a 3.6-fold increase in potency of valproate as its ED50 value on co-administration DHA and VPA against seizures induced by PTZ. Moreover, a 4.9-fold increase in potency of lamotrigine occurred, as its ED50 value against generalized kindled seizures induced by rapid amygdala kindling. COMPUSYN analysis confirmed a synergistic interaction in anticonvulsant activity between DHA and both AEDs: valproate and lamotrigine [13]. This finding shows the need of further preclinical and clinical studies on safe natural anticonvulsant agents like DHA as a component of combination therapy of epilepsy. Furthermore, in recent years there are some reports regarding the central effects of effective natural agent. So, it seems to be useful that the combination therapy of effective natural agent with conventional drugs be investigated on another neurological disorders.

In addition, some studies suggest that combining drugs with different mechanisms of action is more effective against seizure than drugs with similar or overlapping pharmacological properties [15]. So, clearing of anticonvulsant mechanisms of effective safe natural agents like DHA could be useful to select the sufficient complementary drugs on combination therapy with increasing the efficacy and tolerability of drugs as a result.

Evidence-Based Medicine (EBM) provides the classified information on the basis of published data for approaching the best clinical treatment decision making [16]. The optimal clinical application of co-administration of AEDs with natural anticonvulsant agents needs to the systematic categories of studies regarding evidence-based medicine (EBM). In this case as well as clinical mono or polytherapy by AEDs [17-21], EBM could constitute aspects such as:

1. The anticonvulsant action mechanism of AEDs and natural anticonvulsant agents.
2. Efficacy, tolerability and side effect of AEDs and natural anticonvulsant agents in monotherapy and co-administration respected to the kind of seizure, age, condition and neurological and cognitive impairment with epilepsy of patient.
3. The pharmacokinetic and pharmacodynamics interaction between AEDs and natural anticonvulsant agents in co-administration.

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References