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

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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 = 1/(Dx1 +2(Dx2)2 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
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