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Ethical issues of using placebo in antiepileptic drugs trials in Asia

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Abstract

Any human trials should be designed and conducted within the ethical framework of the "Declaration of Helsinki" stating that any new agent must be tested against standard, proven therapies when available. In the clinical development of antiepileptic drugs, a double-blinded, placebo-controlled study is generally considered the gold standard for establishing their clinical efficacy. However, placing patients with epilepsy on placebo is unethical because of negative impact of subsequent seizures resulting from "nontherapy". The ethical concern is relatively small in an add-on trial but becomes problematic when a monotherapy is designed. Asia is expected to play a key role for future clinical development of new antiepileptic drugs. Timely action and collaborations of Asian epilepsy communities for advances in future clinical trials seems high in priority.

Clinical development of antiepileptic drugs (AEDs) follows the established pathway of phase 1 to 4 clinical trials.[1,2] The initial phase 1 study is intended to establish the safety and pharmacology of the drug usually in healthy volunteers. Phase 2 study assesses efficacy, and various dosing regimens in patients with epilepsy. Favorable evidence in phase 2 trials leads to phase 3 studies. To obtain a marketing approval, each efficacy and safety end-point needs to be confirmed and replicated in at least two pivotal phase 3 studies. Phase 4 studies, performed after the drug is on the market, are intended to broaden the knowledge about the new AEDs in a wider population and in a practice-oriented setting.

ETHICAL ISSUES RELATED TO CLINICAL TRIALS AND USING PLACEBO

Clinical research is aiming at developing generalizable knowledge to improve health and/or increase understanding of human biology. By placing some people at risk of harm for the good of others, clinical research has the potential for exploiting human subjects. Ethical requirement for clinical research aims to minimize the possibility of exploitation by ensuring that participating subjects are treated with respect while they contribute to the social good.[3] The guidance on the ethical conduct of clinical research was initiated by Nuremberg code[4] and followed by many other documents.[3] Among those, the "Declaration of Helsinki"[5], written by World Medical Association (WMA), is the most widely accepted ethical guideline and has been revised regularly to cope with changing concept of ethical issues related with human research.

Randomized placebo-controlled trials provide unbiased estimates of treatment effect of test drugs. Non-treatment effects (e.g., regression to the mean, Hawthorn effect, placebo effect, etc.) in human studies[6], are usually unpredictable and often large in magnitude to mimic treatment effect. Therefore, most regulatory agencies require placebo-controlled trials to prove the efficacy of test drugs.

However, using placebo in human trials has raised significant ethical concerns. The "Declaration of Helsinki"[5] states that "concern for the interests of the subject must always prevail over the interests of science and society" and " In any medical study, every patient-including those of a control group, should be assured of the best proved diagnostic and therapeutic method". Based on these guidelines, any control group should be given the best established treatment and a placebo-arm cannot be used when evidence for an adequate treatment effect of testing drugs is known, which have generated hot debates about conducting scientifically valid trials. Recent version (2002) of the "Declaration of Helsinki" clarified this issue by saying that the use of placebo is acceptable only in studies where no proven effective methods exists (e.g., first unprovoked seizure) or if there

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are compelling and scientifically sound reasons for their use under the condition of patients subjected to placebo being assumed of no serious or irreversible harm (e.g., absence seizures).[7]

ETHICAL ISSUES RELATED WITH CLINICAL TRILAS OF ANTIEPILEPTIC DRUGS

In clinical development of new AEDs, an adjunctive treatment in refractory partial seizures is the standard approach seeking for initial marketing approval and the filing for monotherapy indication usually starts late in their development stage. This sequence of AEDs development is certainly at distance from the current clinical view favoring monotherapy, which is related to underlying ethical concerns and the policy of regulatory authorities.[8]

The placebo-controlled add-on therapy of new AEDs in refractory partial epilepsies has been considered ethically justifiable because patients are already under maximally effective therapy and their allocation into placebo-arm may not do any harm. However, in monotherapy trials for regulatory purposes, randomizing patients to placebo arm raises serious ethical concerns due to negative impact of subsequent seizures (e.g., serious physical injury, loss of driving license, jobs, independence, etc.) resulting from "nontherapy". For that reason, monotherapy trials of new AEDs in drug naïve patients have used active drugs as control with their results showing equivalent efficacy between two treatment arms.[7,8] The demonstration of equibalance in efficacy between new and conventional AEDs (non-inferiority), is not accepted as an indication for monotherapy by the US (the European agencies accept them, provided the noninferiority margin is acceptable and the study is powered accordingly).[2] The policy of superiority trial by the US have generated a number of innovative designs of monotherapy trials (Table 1).[7]

Protocols of short-term regulatory monotherapy trials adopted the concept of "pseudoplacebo (low dose of the study drug or suboptimal doses of a standard AED)"and strict "exit criteria" to demonstrate a higher therapeutic failure in the pseudoplacebo arm compared to the high-dose arm. The rational for adopting pseudoplacebo is that a low dose may protect against catastrophic seizures but have little effect on the overall number of partial seizures, which have never been studied adequately.[7] These short-term monotherapy trials have been the subject of intense criticisms related to their low scientific validity and ethical concerns.[8]

Another approach to overcome the ethical concerns in monotherapy trials is using "historical control" instead of placebo (or pseudoplacebo). However, a review of previous data from placebo controlled trials of new AEDs showed that the efficacy of the placebo arm was too variable and large in magnitude (20%-50% of new AEDs) to apply in AEDs trials.[8]

Table 1: Sequence of clinical trials of new antiepileptic drugs

I. For marketing approval (phase 3)
   -Double-blind, placebo-controlled (DBPC) randomized add-on trials in refractory partial epilepsy in adults (at least 2 independent trials)
II. After marketing approval (phase 4)
   1. DBPC, randomized add-on trials in refractory partial epilepsy of children
   2. DBPC, randomized add-on trials in refractory GTCS
   3. Trials in various epilepsy syndromes and special patient groups
   4. Monotherapy trials
      (1) Short-term regulatory trials in refractory epilepsy*
         - presurgical withdrawal study (in-patient)
         - conversion to monotherapy study (out-patient)
      (2) Long-term trials
         - drug substitution in refractory epilepsy
         - active drug controlled study in drug-naïve patients
         - lower-dose controlled study in drug-naïve patients**

DBPC: double-blind placebo-control, GTCS: generalized tonic-clonic seizures
*usually conducted to prove the superiority of study drug compared to low dose (or subtherapeutic dose) of active drugs (pseudoplacebo)
** usually conducted to prove a differences in efficacy between good therapeutic dose and a dose thought to be marginally effective in a more generalizable patient population with fewer seizures since diagnosis.

ETHICAL ISSUES FOR ANTIEPILEPTIC DRUG TRIALS IN ASIA

Asia is the largest continent characterized by great heterogeneities in socioeconomic status and there are many regions being considered as "developing countries". The concept of best treatment, etiology, or demography of epilepsy in developing countries may be quite different and the results of new AEDs trials conducted from the developed countries may not be directly extrapolated to the developing world. Although clinical trials of new AEDs may be necessary to improve epilepsy care in developing countries, shortages of medical personnel qualified to conduct trials and high cost of new AEDs limiting their continuing availability to the community are important factors to consider. Therefore, controlled trials of new AEDs are considered not high in the priority (low social value).[9]

Over the past decade, Asian epilepsy communities have been quite progressive and are participating more frequently to the international collaboration for clinical trials of new AEDs. Furthermore, Asia is expected to play a key role for future clinical development of new AEDs for many reasons; (i) a large pool of patients, (ii) improving standard of clinical practice and scientific basis, and (iii) ever increasing demand of earlier completion of clinical trials by pharmaceutical industries due to limited duration of licenses, etc. Timely action and collaborations of Asian epilepsy communities for advances in future clinical trials seems high in priority.

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