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Special Communication

Prevention of epilepsy: Should we be avoiding clinical trials?

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ABSTRACT

Epilepsy prevention is one of the great unmet needs in epilepsy. Approximately 15% of all epilepsy is caused by an acute acquired CNS insult such as traumatic brain injury (TBI), stroke or encephalitis. There is a latent period between the insult and epilepsy onset that presents an opportunity to intervene with preventive treatment that is unique in neurology. Yet no phase 3 epilepsy prevention studies, and only 2 phase 2 studies have been initiated in the last 16 years. Current prevailing opinion is that the research community is not ready for clinical preventive epilepsy studies, and that animal models should first be refined and biomarkers of epileptogenesis and of epilepsy discovered before clinical studies are embarked upon. We review data to suggest that there is basis to do epilepsy prevention studies now with the current knowledge and available drugs, and that those studies are feasible with currently available tools. We suggest that a different approach is needed from the past in order to maximize chances of success, minimize the cost, and set up platform for future preventive treatment development. That approach should include close coordination of preclinical and clinical development programs in a combined PTE prevention strategy, consideration of polytherapy, and simultaneous, combined clinical development of preventive treatment and of biomarker discovery. We argue that the currently favored approach of eschewing clinical studies until biomarkers are available will delay the discovery of epilepsy prevention treatment by at least 10 years and significantly increase the cost of such discovery.

1. Introduction

Epilepsy prevention is one of the great unmet needs in epilepsy. Approximately 15% of all epilepsy is caused by an acute acquired CNS insult such as traumatic brain injury (TBI), stroke or encephalitis [1] in the Western world, possibly up to 60% in the developing countries, due to a large percentage of infection-related epilepsy [2]. The insult is followed by epilepsy after a period of days, months and sometimes years. This latency period offers an opportunity to intervene after the injury with treatment to prevent epilepsy. This opportunity is unique among neurological diseases. TBI and stroke patients present to medical care early, often within hours, allowing early preventive intervention. 5% of all epilepsy (10% of all acquired epilepsy) is due to TBI [1], with 20,000 new patients a year with post-traumatic epilepsy (PTE) in the US [3]. Preventive treatment could help these patients.

The importance of epilepsy prevention is recognized by the epilepsy community. At the first NIH "Curing Epilepsy" conference in 2000, organized to identify areas of greatest unmet need for immediate research efforts, prevention of epilepsy was among the topmost priorities. The conference/NIH set among its top goals to "…create new treatment for preventing epilepsy…", with a specific benchmark to"Complete at least two major, multi-center trials" [4]. Yet in the intervening 17 years, there has been no new phase 3 preventive study. The NIH has funded only one new clinical epilepsy prevention study since 2000 a successful phase 2 study of PTE prevention using levetiracetam [5],with another phase 2 study funded by the department of defense (DOD) (NCT00598923). The enthusiasm for epilepsy prevention of the early 2000s [6] has been replaced by a belief that preventive studies cannot currently be done. At the most recent, third, NIH CURE for epilepsies conference in 2013, the goals and benchmarks for epilepsy prevention focused exclusively on pre-clinical epileptogenesis, biomarkers, and animal models [4]. The 2000 goal of human preventive studies has disappeared. Recent epilepsy-specific requests for proposals by the NIH and the DOD *discouraged* applications for clinical preventive studies.

Reasons given for this retreat from clinical epilepsy prevention research are that (1) there have been a large number of epilepsy prevention studies, all failed; (2) there are no drugs to test; (3) we do not understand epileptogenesis and therefore do not have therapeutic targets; (4) we need first to test all treatment in rigorous animal in vivo PTE models; (5) the studies are too difficult to do and not feasible; (6) we therefore first need to develop biomarkers to identify treatment targets and improve feasibility of preventive studies; and (7) the studies are too costly and funds for them are not available [7].

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Further, the failure of numerous TBI neuroprotection studies has added to the sense of futility of doing any clinical TBI intervention studies, and to withdrawal of support for them. The goals of the research community and of funding agencies have moved from clinical prevention to the development of animal models and of biomarkers.

In this article, we present the argument that there is basis to do epilepsy prevention studies now with the current knowledge and available drugs, that those studies are feasible with currently available tools, but that we should take a different approach from the past in order to maximize chances of success, minimize the cost, and set up platform for future preventive treatment development. We focus here on *prevention* of epilepsy, rather than on other potential disease modifying treatments aimed at reducing severity of epilepsy, slowing down progression of the disease, and targeting development or modification of comorbid conditions such as cognitive impairment or psychiatric diseases that have recently been discussed as other potential targets of antiepileptogenic treatments [8,9].

2. Historical background

The argument that there has been a large number of failed PTE prevention studies and that such studies are not feasible can be disputed.

2.1. Failed studies

While there have been over 30 randomized phase 3 clinical trials (RCT) of neuroprotection after TBI, there have only been 10 randomized clinic trials ever of PTE and epilepsy prevention [10,11]. Moreover, only 3 studies have been done since 1985, and only 2 since 1990 [11–14]. Only 5 drugs have ever been tested: phenobarbital, phenytoin, carbamazepine, valproate and magnesium. Of these, two, phenytoin and carbamazepine, have no antiepileptogenic activity in animal models. Two more, phenobarbital and valproate, have anti-epileptogenic effects but only in doses ≥2-fold higher than clinically applicable maximum dose [15,16]. The fifth, magnesium, has only been evaluated in Mg-deficient tissue culture, the significance of which for in vivo animal or human epileptogenesis is uncertain. Furthermore, the phase 3 study treatment lasted only one week. There has never been a phase 3 epilepsy prevention study done with a drug with demonstrated pre-clinical antiepileptogenic effect in a clinically applicable dose.

2.2. Feasibility

The 3 most recent phase 3 studies, of phenytoin, valproate and magnesium, done, respectively, in 1980s, 1990s and early 2000s, were all rigorous studies using standard randomized, placebo (PBO)-controlled, double-blind design, adequately powered, with meticulous execution [12–14]. The studies enrolled 379–499 subjects over a period of 4–6 years at one center, with injury to treatment window of 8–24 h. More recently, a phase 2 PTE prevention study with 8 h injury-to treatment window was also successfully completed [5]. All these studies had 24 month follow up duration, with loss of follow up rate ranging from 20 to 28%. The logistic success of these studies shows that PTE prevention studies are feasible.

3. Challenges of clinical PTE prevention studies

Challenges to clinical PTE prevention development include the fundamental, of incomplete understanding of epileptogenesis of PTE and of availability of drugs for clinical testing; and the logistical, of subject recruitment, sample size and long follow up requiring long and costly studies. Linking the two, there is need for better alignment of preclinical and clinical development.

4. Pathophysiology of epileptogenesis

While knowledge of TBI and of PTE epileptogenic processes is only partial, a significant amount is known, and a substantial number of drugs have been successfully tested in animal PTE and other epileptogenic models [17,18]. Putative mechanisms of epileptogenesis have been extensively reviewed [9,19].

The immediate impact of trauma on the brain, the primary injury, causes mechanical damage with shearing and tearing of neurons, glia and axons, breach of blood vessels, extravasation of blood and cell death. This occurs within minutes of the injury. It is followed by secondary injury, which starts within minutes and lasts for days to weeks, possibly months. This includes hypoxia, release of glutamate from destroyed, damaged, and activated neurons and glia resulting in glutamate-mediated excitotoxicity, and inflammation with invasion of brain/subdural space by blood-borne leuko- and lymphocytes, glial cell (microglia and astrocyte) activation, and upregulation of inflammatory mediators such as pro-inflammatory cytokines. These processes result in mitochondrial oxidative stress, energetic failure and accumulation of free radicals. In addition, extravasated blood deposits iron in the parenchyma, adding to free-radical accumulation, and albumin, exacerbating the inflammatory response [20–24]. All this results in cell injury and death from both apoptotic and non–apoptotic mechanisms [20]. Secondary injury is accompanied and followed by repair and recovery, with neuronogenesis, axonal sprouting, dendritic arborization, synaptogenesis, and change in composition of neurotransmitter receptors and neuronal and astroglial ion channels [21–25].

Cell loss results in early, preferential loss of small inhibitory GABAergic neurons in the cortex or the hippocampus [25,26] which are particularly vulnerable to hypoxic/oxidative stress-related injury. This may occur in the first day or two after injury. It results in disinhibition of the principal excitatory neurons, such as the pyramidal cells of cortical layer 5, the CA1 hippocampal pyramidal cells or the granule cells of the dentate gyrus, their increased activity, activity-driven axonal sprouting and synaptogenesis [25,27]. These principal excitatory cells which are normally not connected to each other sprout axon collaterals and form excitatory synapses with neighboring excitatory cells, creating increased excitatory connections, recurrent excitatory circuits and increased synchronization of activity [25–28]. The loss of small inhibitory interneurons reduces inhibition of these hypersynchronized, hyperexcitable networks. The increased neuronal excitability and synchronization results in lowered seizure threshold and epilepsy. In addition, neuronogenesis occurs, and may result in ectopic nodules of neurons with aberrant excitatory connections and more hyperexcitabtle circuits [29,30]. Numerous molecular changes have been implicated in these

Table 1
Examples of approved medications with antiepileptogenic effects in animal models.

MOA	Drug	Model
Antioxidant	α − tocopherol	PTE: Fe injection
	Zonisamide	Same
Antiglutamatergic	Desferroxamine	Same
	DHEA	Same
	Ceftriaxone	PTE: FPI[a]
Anti-inflammatory	Celexocib	SE: Li-pilo[b]
	Losartan	PTE: albumin
	Fingolimod	SE: Li-pilo
Regeneration	Rapamycin	PTE: CCI[c]; SE, TS[d]
	Erythropoeitin	SE, FS
	Gabapentin	PTE: undercut
Pleuripotent	Levetiracetam	PTE: CCI; Kindling; Genetic; Audiogenic
		SE: Li-pilo

[a] FPI = fluid percussion injury.
[b] SE li-pilo = lithium-pilocarpine-induced status epilepticus.
[c] CCI = controlled cortical impact.
[d] TS = tuberose sclerosis.