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Pharmacological Prophylaxis of Post-Traumatic Epilepsy

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Contents

Abstract

Early and late epileptic seizures are a frequent complication of severe head traumas. The administration of anticonvulsant drugs immediately after head injury is commonly implemented as a prophylactic measure; however, there is a lack of consensus on the usefulness of prophylaxis with anticonvulsants for the prevention of late post-traumatic epilepsy (PTE). The inconsistent evidence accumulated so far from clinical studies, most nonrandomised and uncontrolled in design, and the limited knowledge of the processes underlying post-traumatic epileptogenesis, do not warrant empirical pharmacological prophylaxis with long term administration of conventional anticonvulsants. Phenytoin and phenobarbital (phenobarbitone) are used to a large extent in this indication. As a general rule, a benefit/risk analysis in individual patients should drive prophylactic drug prescription in PTE as it can have potential detrimental effects on a patient's recovery. New compounds, such as free-radical scavengers and antiperoxidants, show encouraging experimental results, but their clinical use is still very limited.

Despite its high clinical relevance, pharmacological prophylaxis of post-traumatic epilepsy (PTE) remains a controversial issue in the field of epilepsy.

A surgical approach to patients with established PTE was in place[1] until the topic was highlighted in the early 1950s, following World War II.[2] The higher number of individuals who survived combat during this war and who developed PTE, compared with World War I, strengthened the need for an appropriate drug prophylaxis of PTE. Good results were achieved at that time with the anticonvulsant phenytoin.[3,4] Following experimental evidence of a protective effect of phenobarbital (phenobarbitone) on aluminium-induced audiogenic seizures in rats,[5] a model that was considered close to human PTE, many papers were published which consistently showed positive results with drug prophylaxis of

PTE using either phenobarbital or phenytoin.[6-14] However, disappointing conclusions were later drawn from larger *ad hoc* designed prospective studies, which triggered scepticism of this practice and seeded indecision in clinical conduct.[2,15-18] Failure of phenytoin in a large, randomised, controlled study in PTE further stimulated debate and controversy among clinicians.[19]

These conflicting results have triggered the publication of several reviews of the topic, in an attempt to: (i) bring together and evaluate the available data; and (ii) suggest an evidence-based approach to the pharmacological prophylaxis of PTE.[20-33]

1. Definition

Three kinds of seizures can complicate severe head injury and these are distinguished by the time-interval following trauma: (i) impact seizures, appearing within 24 hours; (ii) early seizures, occurring within 1 week; and (iii) late seizures, observed from day 8 through to 2 years, but frequently later.[34-36] Other seizures, such as concussive convulsions frequently observed in sports, are not epileptic in nature, have symptoms similar to those of convulsive syncope and do not require treatment.[37] In children, benign epileptiform discharges are often observed after head trauma, but they show a favourable prognosis without treatment.[38]

Seizure type also varies with time-period after head injury, with a relatively high proportion of generalised seizures at an early stage and a progressively larger prevalence of partial seizures later.[36] Early occurrence of status epilepticus has been reported to be as high as 20% and, therefore, should not be neglected.[39] As a consequence, the choice of anticonvulsant needs to be tailored in accordance with seizure type.

Ideally, prophylaxis should aim at reducing the chance of developing PTE with drug treatment or with other actions which affect its pathogenesis.[28] Such preventative therapy should inhibit the processes involved in the induction of PTE. Therefore, anticonvulsant prevention of early seizures after severe head trauma – to avoid complications from hypertension and hypoxia associated with convulsive seizures – needs to be differentiated from prophylaxis of late seizures following severe head trauma, which aims at interfering with epileptogenesis. The latter is the process by which abnormal neuronal functional reorganisation occurs, ultimately leading to excessive neuronal circuit excitability and appearance of clinical seizures.

2. Early Post-Traumatic Seizures

In a series of 3340 adults with severe closed head trauma, an early seizure frequency of 3.6% has been reported, with 1.26% occurring within 24 hours.[40] The presence of intracerebral parenchymal damage on computed tomography scan after severe closed head injury did not increase the risk of early post-traumatic seizures. The occurrence of early seizures did not affect neurological recovery.[35,40] However, seizures occurring early after head trauma worsen both intracranial hypertension and associated hypoxia in injured tissue. Therefore, administration of anticonvulsants needs to be initiated as early as possible in patients with severe head trauma. Apart from an uncontrolled trial, with conflicting results depending on analysis,[41,42] and negative results reported in a double-blind, placebo-controlled trial with phenytoin[43] (perhaps biased by a wide confidence interval among observed outcomes), all other published results show that pharmacological control of early seizures with phenytoin, phenobarbital, valproic acid (sodium valproate) and carbamazepine is effective.[20,44-46] Anticonvulsants were administered first parenterally (phenobarbital 200 mg/day, phenytoin 500 to 750 mg/ day, valproic acid 30 mg/kg/day, and carbamazepine 300 to 600 mg/day orally as it is unavailable in intramuscular/ intravenous formulations) and then treatment was switched to the oral route as soon as this was feasible.[20,44-46]

Careful blood monitoring of anticonvulsant concentrations should drive frequent adjustments of dose to achieve optimal drug concentrations, i.e. so that they are in the therapeutic range and to avoid toxicity. Kinetic alterations of either carbamazepine, phenytoin or valproic acid have been detected in patients with traumatic injury. In this condition

valproic acid and phenytoin protein binding is reduced[47,48] and carbamazepine kinetics altered.[49] Inadequate blood concentrations of anticonvulsants can be related to the hypermetabolic state of injured patients, and thus it is advisable to keep drug concentrations in the higher end of the therapeutic range.

3. Late Post-Traumatic Seizures

The appearance of seizures late after head injury is a major residual complication and an event that is difficult to predict. Late PTE complicates head trauma in about 7% of civilians[50] and 34% of combat-injured patients,[51] increasing up to 50% in patients with severe neurotrauma.[52,53] Annegers et al.[50] found the risk for late PTE to be 0.1% at 1 year and 0.6% at 5 years after a mild trauma, 0.7% at 1 year and 1.6% at 5 years after a moderate trauma, and 7.1% at 1 year and 11.5% at 5 years after a severe trauma.

Lack of knowledge of definite mechanisms underlying the development of PTE during the so-called 'maturation of epileptic focus', seriously affects the ability to provide a rational prophylactic strategy, or even one at all. That mechanisms of epileptogenesis and seizures might be different has to be considered. The proper identification of processes producing post-traumatic epileptogenesis is fundamental to applying effective drug treatment.

3.1 Prediction of Late Seizures

Experimental data from animals given anticonvulsants to prevent PTE are limited. Further, their relevance for humans is uncertain. The lack of comprehensive experimental studies evaluating the efficacy of drug prophylaxis is related to the lack of appropriate PTE animal models. Servit[5] used a model of audiogenic seizures in rats, which was thought to reproduce PTE, induced by local application in the forebrain cortex of aluminium hydroxide. In his experiment, phenobarbital significantly reduced the number of animals with epilepsy. In a similar experimental model in monkeys, a preventive effect with orally administered phenobarbital and phenytoin has been shown.[54,55] Rapport and Ojemann,[56] using chronic cobalt-induced epilepsy in cats, proved the prophylactic effect of phenytoin. In rats receiving $FeCl_2$ 10μL or saline by injection into the isocortex, phenytoin prevented occurrence of both convulsive and electroencephalogram (EEG) seizures.[57]

The pathology of PTE does not provide any assistance in interpretation of epileptogenic mechanisms.[58] It shows nonspecific neuronal loss, cavitarian necrosis, iron-filled macrophages, glial and fibroblastic reaction, and synaptic rearrangement with sprouting. However, the kindling hypothesis, with formation of new neural connections through sprouting, leading to abnormal excitability, repetitive neuronal firing and a kindling process culminating in epilepsy, does support the use of established anticonvulsants. Recurrent axon collaterals are newly sprouted by pyramidal cells connected by an excitatory synapse as a consequence of axonal injury, and suggest that this process underlies the development of PTE.[59,60]

A pragmatic approach to the problem, encompassing the limited knowledge of epileptogenic mechanisms, is to advocate surrogate tools, i.e. clinical variables associated with risk of developing PTE, and the use of conventional anticonvulsants.

3.1.1 Risk Factors

Prediction of late PTE by identification of its risk factors has been widely explored.[9,61-63] Late PTE occurs in over 30% of patients with penetrating head injuries, intracerebral or subdural haematoma, depressed skull fracture, or early seizures after injury.[50,53] PTE seems generally related to brain trauma severity, extent of tissue loss and the penetrating nature of the trauma, in other words to 'brain trauma dose'.[64-66] Dural penetration increases the occurrence of PTE from 20 to 57%.[64]

Features of acute injury have been recently investigated in 57 PTE patients after severe head trauma compared with 50 non-PTE patients.[39] Injury variables significantly associated with late PTE were: loss of consciousness, focal neurological signs at first examination, missile injuries, frontal lesions, intracerebral haemorrhage, diffuse cerebral contusions, prolonged (>3 days) post-traumatic amnesia, cortical-subcortical lesions and depressed skull

fracture. A combination of the last 3 variables significantly enhances the risk of PTE.

3.2 Experience With Traditional Anticonvulsants

Even though the risk factors predicting the chance of developing late epilepsy after head trauma are well recognised, we still lack guidelines supporting whether, and how, to instigate pharmacological prophylaxis.

Some authors have suggested capitalising on experience with anticonvulsant prophylaxis of late seizures following cranial surgery.[67] In 12% of children undergoing subfrontal craniotomy, seizures appeared within ≤3 years. Anticonvulsants were ineffective in reducing the incidence of postoperative seizures.[68] Although positive results with phenytoin have been reported,[69] a recent review of 30 publications (including 6 controlled trials) on the topic, has shown that prophylactically administered anticonvulsants tend to prevent postoperative epilepsy but that this effect is certainly not statistically significant.[70]

A large amount of clinical research has been undertaken in the attempt to find the best drug strategy to prevent PTE.[71-78] As well as a limited number of controlled trials showing effective and ineffective use of valproic acid [79,80] and carbamazepine,[44,81] the use of phenobarbital and phenytoin has provided contradictory results (table I). In fact, most of the positive studies were nonblind studies, whereas most of the negative studies were randomised and controlled. The majority of papers are based on personal experience, retrospective analysis and prospective uncontrolled observation. A meta-analysis of both published and unpublished controlled trials was hampered by the differences in classification and choice of patients, drug dosage and treatment duration.[32]

Among the latest generation of anticonvulsants, only vigabatrin has been evaluated in this indication. Vigabatrin has been shown to induce some protective effect in an experimental model of PTE.[82]

Table I. Published results of drug prophylaxis of late post-traumatic seizures with phenobarbital (phenobarbitone) and phenytoin

Drug	References[a]
Phenobarbital	
Positive results	3, 6, 7, 9, 11-13, 77
Negative results	2, 15, 21, 78
Phenytoin	
Positive results	3, 4, 7, 8, 10, 13, 14
Negative results	2, 15-19, 21, 42, 53, 65, 71

a When reported twice, reference refers to a trial including administration of both phenobarbital and phenytoin.

3.3 Alternative Approaches

Alternative pharmacological approaches to PTE prophylaxis are being pursued on the basis of putative pathogenetic models of post-traumatic epileptogenesis. The iron hypothesis, which predominates among others, implicates iron-induced oxidative stress, delayed tissue damage and neuro-toxicity following traumatic brain injury in the aetiology of PTE. In head trauma, blood extravasation causes deposition of ferrous compound into neural tissue and the Haber-Weiss iron-catalysed reaction, with hyperproduction of hydroxyl radicals. These reactive oxygen-derived species (ROS) trigger subsequent formation of peroxidative agents (free radicals), which in turn cause a self-sustained lipid peroxidation of phospholipid membranes and disruption of the cell wall leading to cell death.[83] The induction of an epileptic focus by iron deposition is also related to a decreased nitric oxide synthase activity.[84] Furthermore, ROS impair glutamate transport into astrocytes, with a consequent excessive accumulation of this excitatory amino acid in the extracellular space.[83] By limiting initiation and propagation of lipid peroxidation, brain injury response and, thereby, post-traumatic epileptogenesis might be prevented. In fact, the common reactive gliosis would express the enhanced neuroprotective role of astrocytes, consisting of an increase in the natural antioxidant defence of neurons.

Endogenous natural antioxidant defences include superoxide dismutase (SOD), glutathione peroxidase, catalase, tocopherol (α-tocopherol, vitamin E), glutathione, ascorbate (reduced vitamin C) and

adenosine.[85] However, these agents seem largely unable to limit processes leading to PTE occurrence.

Adenosine and 2-chloroadenosine have scavenging effects on hydroxyl radicals and superoxide. In an animal model, both suppressed the occurrence of epileptic discharges induced by FeCl3 injection.[86] Adenosine, which is released from nerve-glial cells in large amounts after ischaemia, counteracts the generation of burst discharges, an effect ascribed to a modulation of dendritic membrane properties. This protective action may be inhibited by adenosine receptor antagonists, such as theophylline, which in turn enhance postischaemic nerve cell death.[86]

The early use of the antioxidant methylprednisone showed limited ability to present both epilepsy and peroxidation.[57] Tocopherol prevented both peroxidation and epilepsy caused by iron injection into hippocampus in rats,[87] as did phenobarbital.[88]

Since traditional antioxidants have limited efficacy in preventing/reversing brain damage, several new compounds are under different stages of experimental and clinical evaluation in this indication. So-called neuroprotective agents, preventing one or multiple events through the previously mentioned hypothetical sequence of mediators, are being investigated in experimental models and in limited groups of patients (table II).[89-110]

To prevent damage from calcium overload, the calcium antagonist nimodipine, a strongly lipophilic agent, has been tried but with limited benefit.[111-113] An early exposure to tetrodotoxin, a potent sodium channel blocker, has been shown to prevent the cascade of molecular events leading to epileptogenesis in rats.[114] Initial results with tirilazad, a potent inhibitor of lipid peroxidation, have shown encouraging results but trials are still in progress.[96] Free radical scavengers, such as polyethylene glycol (PEG) monomers with SOD or PEG-catalase, have demonstrated beneficial activity in animal models.[91] TJ-960, a Japanese herbal medicine, has scavenging activity for free radicals generated within an iron-induced epileptogenic region of rat brain.[98]

All these non-anticonvulsant compounds may represent future pharmacological interventions, aimed at limiting damage caused by reactions underlying epileptogenesis; however, their clinical application is very limited at present.

Table II. New compounds currently assessed in experimental models of post-traumatic epilepsy and their mode of action

Compound	Mechanism of action	Reference
Selfotel	Glutamate antagonist	95
Aptiganel	Glutamate antagonist	105
Eliprodil	Glutamate antagonist	92
Lubeluzole	Glutamate antagonist	106
Licostinel (ACEA-1021)	Glutamate antagonist	97
Gavestinel (GV-150526)	Glutamate antagonist	102
Sipatrigine (619C89)	Glutamate antagonist	100
Nalmefene	κ-Opiate antagonist	103
Tirilazad	Lipid peroxidation inhibitor	90
Montirelin (CG-3703)	Protirelin (thyrotrophin-releasing hormone;TRH) analogue	103
S-Nitrosoglutathione	Antioxidant	110
MDL-74180	Tocopherol (vitamin E) analogue	99
OPC-14117	Superoxide radical scavenger	104
Pergorgotein (PEG-SOD)	Superoxide radical scavenger	91, 101
TJ-960	Superoxide radical scavenger	98
Dizocilpine (MK-801)	Superoxide radical scavenger	109
Melatonin	Superoxide radical scavenger	108
EUK-8	Superoxide radical scavenger	94
EUK-134	Superoxide radical scavenger	107
NG-Mono-methyl-l-arginine (NMMA)	Nitric oxide synthesis inhibitor	93

Table III. Head trauma and post-traumatic seizures. Sample size consideration for a clinical trial. This table gives the sample size considerations for 3 hypothetical studies (a, b, c). If we wished to detect a 50% decrease in the incidence of post-traumatic epilepsy in a study including all moderate and severe head injuries, that study would require 2000 patients. Based on Olmsted County, Minnesota, USA, incidence rates of moderate head injuries eligible for such a study, the underlying population necessary to generate sufficient patients would be about 2.6 million over a period of 1 year (column a). If the study is restricted to severe head injuries the sample size needed to detect a 50% decrease is reduced to 800, but the population base is increased to 5.1 million because of the lower incidence of severe injuries (column b). Column c shows the difficulties in detecting a modest decrease in incidence of only 20%. If one wished to detect such a decrease, 8000 severe head injuries would be necessary, which would require a population base of 50.7 million (reproduced from Annegers,[116] with permission)

	a	b	c
Risk in untreated	0.05	0.1	0.1
Decrease in treated	0.5	0.5	0.2
Type I error	0.05	0.05	0.05
Type II error	0.2	0.2	0.2
Number of patients needed	2000	800	8000
Population required to obtain number (in millions)	2.6	5.1	50.7

4. Conclusion

Control of seizures immediately following traumatic head injury is satisfactorily achieved by short term administration of the established anticonvulsants, a prophylactic measure widely implemented in clinical practice. In contrast, no acceptable effective prophylactic strategies are to date in place to inhibit late epileptogenesis following severe head trauma. This is primarily because of conflicting results accumulated in uncontrolled clinical trials, retrospective observations and a limited number of double-blind, placebo-controlled studies. Therefore, it is imperative to carry out additional prospective, randomised, controlled studies, statistically powered to detect significant differences. To this goal, a more precise definition of objectives, selection criteria, study design, outcome measures, timeframe assessment and medication is mandatory.[115] However, a large study sample size is necessary to obtain statistically significant results, and this factor definitely represents the major limitation to the initiation of such trials (table III).

Universal prophylactic anticonvulsant use in PTE is at present not recommended.[117,118] Nevertheless, current clinical practice widely differs from this. A recent survey in 127 neurosurgical departments has shown the following attitude towards PTE prophylaxis: 36% of neurosurgeons do not prophylactically treat any injured patients and 12% of them prescribe prophylactic anticonvulsants in any trauma. The remaining 52% of surgeons make a decision on an individual patient's need, based on existing risk factors (penetrating injuries, intracranial haemorrhage, EEG abnormalities, etc.).[119]

A practical approach to this unsolved problem would be to continue administration of anticonvulsants beyond the acute period only in individual patients in whom a high risk of developing late PTE can be predicted by the severity of trauma. The decision should include a benefit/risk assessment before establishing long term anticonvulsant prophylaxis.[31,120,121] The primary goal is to ensure a beneficial or at least neutral impact of drugs on post-injury functional recovery, a goal which is currently not acheived with conventional anticonvulsants.[122-124]

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