LEADING ARTICLE

Drugs 2001; 61 (8): 1045-1055
0012-6667/01/0008-1045/$27.50/0

Antiepileptogenic Agents
How Close Are We?

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Abstract

Epilepsy is a common neurological condition, affecting about 4% of individuals over their lifetime. Epilepsy can be idiopathic, secondary to an underlying genetic abnormality or unknown causes, or acquired. Known potential causes account for about one third of epilepsy. Control of epilepsy has primarily focused on suppressing seizure activity after epilepsy has developed. An intriguing possibility is to control acquired epilepsy by preventing epileptogenesis, the process by which the brain becomes epileptic. Many laboratory models simulate human epilepsy as well as provide a system for studying epileptogenesis. The kindling model involves repeated application of subconvulsive electrical stimulation to the brain, leading to spontaneous seizures. Other models include the cortical or systemic injection of various chemicals. These models suggest that many antiepileptic drugs, from phenobarbital and valproate (valproic acid) to levetiracetam and tiagabine, have antiepileptogenic potential. Some promising other possibilities include N-methyl-D-aspartate (NMDA) or alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) antagonists as well as the neurotrophins and their receptors.

Phenobarbital, phenytoin, valproate, carbamazepine and, to a very limited extent, diazepam have been evaluated in clinical trials to test whether they actually prevent epileptogenesis in humans. Results have been very disappointing. Meta-analyses of 12 different drug-condition combinations show none with significantly lower unprovoked seizure rates among those receiving the active drug. In 4 of the 12, the observed rate was actually slightly higher among treated individuals. None of the newer drugs have been evaluated in antiepileptogenesis trials. Until some drugs demonstrate a clear antiepileptogenic effect in clinical trials, the best course to reduce the incidence of epilepsy is primary prevention of the risk-increasing events — for example, wearing helmets, using seat belts, or decreasing the risk of stroke by reducing smoking.

The incidence, aetiology and types of seizure disorders are age-dependent. The onset of epilepsy in children is predominantly idiopathic, presumably genetic or with no known underlying aetiology. In children, generalised seizures occur more than partial seizures. Epilepsy in the adult population has an increasing incidence of acquired epilepsy secondary to brain tumours, head injury, stroke and central nervous system (CNS) infections with partial seizures the predominant seizure type. After age 35, the incidence of acquired epilepsy is approximately equal to idiopathic epilepsy until age 65 when the incidence of acquired epilepsy exceeds idiopathic epilepsy.[1] Overall, about 30 to 35% of

people with epilepsy have their seizures attributed to a known post-natal cause. This 'remote symptomatic epilepsy' is more difficult to treat successfully and is less likely to go into long term remission than epilepsy without a known cause.[2] Even surgical treatment may be less effective for patients whose epilepsy is caused by head trauma.[3] If this epilepsy could be prevented from occurring by an antiepileptogenic treatment, both human suffering and costs would be reduced.

Early development in antiepileptic drugs focused on seizure suppression and, shortly thereafter, these drugs began to be prescribed in an attempt to prevent epileptogenesis. Epileptogenesis refers to the *acquired* forms of epilepsy and does not involve the predisposition to long term seizures secondary to genetic determination or to abnormalities of brain development.[4] By 1947, results were presented of a clinical trial of phenytoin for an antiepileptogenic use in patients with traumatic brain injury.[5] Many additional studies have taken place since then and the use of drugs for epilepsy prophylaxis became common despite minimal or no evidence of efficacy.[6] This review briefly summarises the laboratory models for evaluating potential antiepileptogenic agents, looks at the current state of knowledge in preventing epileptogenesis in humans, and discusses some promising new agents. Specifically it addresses the question: 'have studies identified agents that can reliably prevent the process of epileptogenesis in people who are at especially high risk for developing seizures?'.

1. Investigative Models of Epileptogenesis and Anti-Epileptogenic Treatment

There are more than 100 *in vivo* and *in vitro* seizure models currently available for epilepsy research as reviewed by Loscher[7] and Fariello.[8] The overwhelming majority of these examine the effects of various chemotherapeutic agents on the prevention of seizures after the process of epileptogenesis has occurred. Despite the marked increase in understanding of epileptogenesis at the cellular and molecular level, and the identification of several targets for potential antiepileptogenic treatment, there are few useful models that specifically facilitate the study of *antiepileptogenesis*.

The pathogenesis of seizures involves multiple pathways at the molecular and cellular level, but the exact mechanism of epileptogenesis, or the progressive changes in neural networks that eventually provoke spontaneous seizures, is poorly understood. At the most basic levels of understanding, critical events in epileptogenesis involve the potentiation of excitatory synapses and depression of inhibitory synapses.[9] Widespread reliance on two primary screening tests has led to the identification of novel compounds that resemble either phenytoin (suppressing high-frequency repetitive firing in cultured neurons and prolonging inactivation of voltage-dependent sodium channels identified by the maximal electroshock test) or benzodiazepines [potentiating the inhibitory effect of γ-aminobutyric acid (GABA), identified by the threshold pentylenetetrazol test]. Both *in vivo* and *in vitro* models are important in the study of the development and expression of focal seizures as well as in the preclinical evaluation of antiepileptic treatment.[10]

A recent *in vitro* study using a rat brain slice model demonstrated that epileptogenesis can be attenuated with the early application of valproic acid. The authors of this report induce epileptiform activity in brain slices by removing the most superficial 450 to 500μm of neocortex.[11] This is not a common model for the study epileptogenesis, but its findings are provocative and suggest a potential role for early anticonvulsant treatment of brain-injured patients.

The hippocampal slice model has dominated *in vitro* studies of epilepsy and epileptogenesis, although its utility for studying epileptogenesis remains controversial. Recently, the hippocampal slice model has been used to classify anticonvulsant drugs into three categories: (i) those that affect basal neuronal excitability but not epileptogenesis (e.g. phenytoin); (ii) those that affect basal neuronal excitability and epileptogenesis (e.g. barbiturates); and (iii) those that affect epileptogenesis but not basal neuronal excitability (e.g. felbamate).[12]

Although these findings demonstrate a potential usefulness of the hippocampal slice model in the study of epileptogenesis, the mainstay of investigative models involves *in vivo* electrical stimulation, or kindling, of the amygdala.[13]

In the kindling model of epileptogenesis, periodic application of an initially subconvulsive electrical stimulus eventually leads to the permanent establishment of an epileptic state.[4,13,14] Numerous variations have been reported since 1969 when Goddard et al. first described a kindling model in the rat amygdala.[15] Examples include using the kindling model in cats[16] as well as the electrical stimulation of the ventral hippocampus or angular bundle.[17,18]

Other useful animal models to study antiepileptogenic treatment include the systemic or intracerebral injection of kainic acid,[19] systemic injection of epileptogenic agents [pilocarpine, N-methyl-D-aspartate (NMDA), picrotoxin, pentamethylentetrazol, strychnine],[12,20-23] and intracerebral injection of tetanus toxin[24] or ferric cations.[25] Each of these *in vivo* models results in the development of spontaneous seizures, which makes them valuable for investigating human epilepsies, epileptogenesis and the prevention of epileptogenesis.

Despite ongoing vigorous research in both academia and industry to develop new antiepileptic drugs using the above models, there is no report of a drug or chemical agent that fully protects against epileptogenesis. Developments in molecular biology have transformed the search for novel therapeutic agents in all areas of pharmaceutical research, and our understanding of acquired forms of epilepsy has also improved.[26] But the overall lack of understanding of the mechanisms involved in epileptogenesis has made pharmaceutical discovery in this area difficult, mostly with regard to adapting laboratory information to clinical usefulness.

The effect on epileptogenesis of conventional therapeutics as well as some of the newer agents is summarised in table I. Some of the agents tested in the models, for example carbamazepine[14] and topiramate,[51] serve as excellent anticonvulsants, but apparently do not attenuate epileptogenesis. On the other hand, valproate (valproic acid), diazepam, phenobarbital and the newer agents tiagabine and levetiracetam have substantial antiepileptogenic effects in the amygdala-kindling model.

Progress in developing 'antiepileptogenic' therapies will require further advances in understanding the mechanistic roles of the various biochemical and anatomical changes in the transformation of normal to hyperexcitable neural networks.[54] Future work will probably define molecular targets for compounds to block or reverse chronic epileptogenesis.[26] Some promising possibilities include NMDA or alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) antagonists[55,56] as well as the neurotrophins and their receptors.[57-59]

2. Human Studies

2.1 Study Designs

All clinical trials of agents to prevent epileptogenesis have had a similar design. Soon after – or occasionally before – an event that greatly increases the risk of developing epilepsy, investigators assign individuals at high risk to treatment with the agent under study or an inactive control. Typically, the drugs are stopped after a period of treatment that may last for years. If the drug has prevented the epileptogenic process from occurring, the treated group should have virtually no epilepsy while the control group has many cases. Even if the drug is only partially effective, after the treatment period has ended, the treated group should have fewer people with seizures than the control group. One would expect to see the effect during the treatment period as well but a drug that suppresses seizures could have a similar effect during the treatment period as one that prevents the epileptogenic process. Evaluation of the epileptogenic effect of a drug is complicated by patients who develop seizures during the treatment period and who then receive long term treatment with seizure-suppressing medications, possibly lessening the difference seen after the study treatment is

Table I. Laboratory models: effect of classic and new drugs on epileptogenesis

Drug	Model	Effect
Carbamazepine	Amygdala-kindled rats	Ineffective[14,27]
	Amygdala-kindled cats	Weakly attenuated[16]
	Pentylenetetrazol-induced kindling in rats	Ineffective[28]
Diazepam	Amygdala-kindled rats	Attenuated[29-32]
	Pentylenetetrazol-induced kindling in rats	Attenuated[28]
Ethosuximide	Pentylenetetrazol-induced kindling in rats	Attenuated[28,33]
Felbamate	Amygdala-kindled rats	Weakly attenuated[34]
Lamotrigine	Homocysteine thiolactone administration	Ineffective[35]
	Amygdala-kindled rats	Ineffective[36]
Levetiracetam	Amygdala-kindled rats	Attenuated[37]
	Corneally-kindled rats	Protected[38]
Phenobarbital	Pentylenetetrazol-induced kindling in rats	Attenuated[33]
	Amygdala-kindled rats	Attenuated[14]
	Amygdala-kindled cats	Attenuated[16]
	Hippocampal injection of penicillin in cats	Attenuated[39]
	Hippocampal injection of penicillin in rats	Attenuated[40,41]
	Alumina-gel injection in monkeys	Ineffective[42]
Phenytoin	Amygdala-kindled rats	Raises seizure threshold but ineffective in preventing epileptogenesis[27,43,44]
	Amygdala-kindled cats	Ineffective[16,45]
	Homocysteine thiolactone administration	Attenuated[35]
	Flurothyl seizures in mice	Attenuated[46]
	Kindling induced by cortical penicillin in rats	Attenuated[40,47,48]
	Alumina-gel injection in monkeys	Mixed[a][42,49]
Tiagabine	Amygdala-kindled rats	Attenuated[50]
Topiratmate	Amygdala-kindled rats	Ineffective[51]
Valproate (valproic acid)	Amygdala-kindled rats	Markedly attenuated[14]
	Pentylenetetrazol-induced kindling in rats	Attenuated[28]
	Flurothyl seizures in mice	Attenuated, retarded reorganization[46]
	Rat brain slice	Mixed[b][11]
Vigabatrin	Amygdala-kindled mice	Attenuated[52]
	Amygdala-kindled rats	Ineffective[53]
	Corneally-kindled rats	Attenuated[38]

a Attenuated with high dose, enhanced with standard dose.

b Attenuated if applied within 20 minutes, ineffective if applied 30 minutes or later.

stopped. The designs of trials that have been conducted in patients after traumatic brain injury are summarised in table II.

2.2 Conditions

Although any condition that raises the risk of seizures potentially could be studied, investigators have generally limited studies to patients who have at least a 20% chance of developing seizures. Below this level, even a perfectly effective drug would be given to over 4 people who would not need to be exposed to the drug in order to benefit one person. Additionally, the sample size needed for clinical trials to detect the same proportionate effect increases as the seizure rate decreases. Table III lists conditions where trials might be done and the approximate percent of patients who develop seizures in the high-risk subgroups.

The most commonly studied groups are patients undergoing supratentorial craniotomy for any rea-

son and people with traumatic brain injury. Symptomatic status epilepticus, for example, that associated with a metabolic cause or anoxic encephalopathy, provides another opportunity.[75] While complex febrile seizures are a risk factor for the later development of epilepsy, this condition is not well suited for antiepileptogenesis trials because of the low seizure rate and long latency before seizures develop. Febrile seizures usually occur in children under the age of 3, but only 2% overall and 10% of the children at high risk (including those with complex febrile seizures) develop epilepsy by age 7.[77] Patients with over 20% risk are rare. Nevertheless, some trials that have been conducted to prevent recurrent febrile seizures have reported results of long term follow-up relevant to antiepileptogenesis.[78-80]

2.3 Study Results

2.3.1 Seizures

Careful evaluation has been limited to only a few drugs, all of which have been marketed for at least 20 years (see fig. 1). The results presented in figure 1 are based on meta-analyses of controlled trials[81] using Mantel-Haenszel analysis for relative risk, or if there is significant heterogeneity among the relative risks for different studies, a mixed effects model (MetaView).[82]

Phenobarbital

Phenobarbital shows antiepileptogenic effects in most of the laboratory models of antiepileptogenesis.

Phenobarbital has been evaluated in 2 studies involving patients with traumatic brain injury.[54,61] As seen in table II, the studies had sub-

Table II. Antiepileptogenesis trials following traumatic brain injury

Active treatment	Control treatment	No. of patients	Time to start drug	Length of treatment	Follow-up including treatment	Late seizure rate (%)	
						active	control
Phenobarbital[60]	Placebo	163	12 hours	6 months	18 months	3	8
Phenobarbital[61]	No treatment	126	1 month	35 months	60 months	16	11
Valproate (valproic acid)[62]	Phenytoin (1 week)	379	24 hours	1 or 6 months	24 months	20	15
Phenytoin[5,63]	No treatment	94	Not stated	4 years	Not stated	6[a]	51
Phenytoin[64,65]	Placebo	244	24 hours	18 months	18 months	12	11
Phenytoin[66]	Placebo	164	1 week	12 months	24 months	10	9
Phenytoin[67]	Placebo	404	24 hours	12 months	24 months	27	21
Phenytoin[68]	No treatment	86	24 hours	3-12 months	24 months	6	42
Phenytoin[60]	Placebo	146	12 hours	6 months	18 months	1	8
Phenobarbital/ phenytoin[69]	No treatment	73	Not stated	2 years	Not stated	0[a]	21
Phenobarbital/ phenytoin[70]	Placebo	125	12 hours	18 months	36 months	23[a]	13
Phenobarbital/ phenytoin[60]	Placebo	49	12 hours	6 months	18 months	14[a]	39
Phenobarbital/ phenytoin[60]	Placebo	152	48 hours	6 months	18 months	24[a]	16
Phenobarbital/ phenytoin[60]	Placebo	148	12 hours	6 months	18 months	3	8
Carbamazepine[71]	Placebo	139	12 hours	24 months	24 months	27	33

a Rate for early and late seizures combined.

Table III. Conditions or procedures with high risk of developing epilepsy

Condition or procedure	High risk subgroup	Seizure rate in high risk subgroups (% patients)
Craniotomy for any reason	Supratentorial	20-50[72,73]
Traumatic brain injury	Penetrating missile wound, intracranial haematoma, cortical contusion, depressed skull fracture, immediate seizure	20-50[60]
Stroke	Haemorrhagic, total anterior circulation infarct, or with early seizure	20-35[74]
Aneurysm or AVM	Anterior or middle cerebral artery, any AVM	20-50[72]
Brain tumour	Resected	20-38[72,73]
Status epilepticus (symptomatic)		40[75]
CNS infection	Viral encephalitis with early seizures	22[76]

AVM = arteriovenous malformation; **CNS** = central nervous system.

stantial differences in design. However, neither shows a significantly positive effect of phenobarbital, even though the evaluation period includes the time during and after treatment. Figure 1 presents the evidence for antiepileptogenesis based on the combined results of both of the studies. The relative risk (RR), that is the ratio of the seizure rate with phenobarbital to that with the control, is plotted with a circle, and the 95% confidence interval (CI) for it is marked by the horizontal line. A relative risk of one indicates equal seizure rates with the active treatment and the control, that is, no antiepileptogenic effect. Figure 1 shows that based on the results of both studies, the best estimate of the relative risk with phenobarbital after traumatic brain injury is almost 1 (RR = 0.98, 95% CI 0.48 to 2.04, p = 1 combining results from the two studies).

Phenobarbital has been studied in patients diagnosed with brain tumour.[83] Those receiving phenobarbital had fewer late seizures (RR = 0.62, 95% CI 0.12 to 3.19, p = 0.6), but the sample size is too small to give reliable results. Patients also received treatment during the entire evaluation period, precluding differentiation of a seizure-suppressing effect from an antiepileptogenic one.

Phenobarbital was also given continuously for several years to prevent recurrent febrile seizures in young children.[84,85] Those children were followed until they were about 8 years old.[79,80] Overall, more children assigned to phenobarbital had afebrile seizures, although the number of children with afebrile seizures was small under both conditions, giving a very low power to detect an effect (RR = 2.69, 95% CI 0.82 to 8.90, p = 0.1).

Valproate (Valproic Acid)

Valproate consistently shows promise for antiepileptogenesis in laboratory models, especially amygdaloid kindling. However, it has been tested in clinical trials of patients with traumatic brain injury, brain tumours and craniotomy, with very disappointing results.

Both the studies in patients with traumatic brain injury[62] and those with brain tumour[86] have higher late seizure rates among those receiving valproate (traumatic brain injury RR = 1.28, 95% CI 0.76 to 2.16, p = 0.4; brain tumour RR = 1.44, 95% CI 0.70 to 2.96, p = 0.4) despite including the treatment period in the evaluation. The traumatic brain injury study used 1 week of phenytoin as a control.

The single study involving craniotomy[87] did not report late (epileptic) seizures separately from early (provoked) seizures. It shows a slightly lower risk of seizures in those receiving valproate (RR = 0.85, 95% CI 0.54 to 1.36, p = 0.5) but the difference does not approach either clinical or statistical significance despite the evaluation period including the early period and the time on treatment.

Diazepam

Diazepam is a drug which looks promising in preventing epileptogenesis in kindling models. Clinically, diazepam is given intermittently to prevent recurrent febrile seizures. In 2 randomised studies diazepam was administered at the time of fever onset. The rate of recurrent febrile and also afebrile seizures was determined.[78,88] Although

the diazepam was effective in these studies in preventing recurrent febrile seizures, essentially the same number of children in each group had afebrile seizures (RR = 0.98, 95% CI, 0.50 to 1.92, p = 0.9). The children were given diazepam only when they developed a fever, so these studies provide a very stringent test for antiepileptogenesis.

Phenytoin

Phenytoin looks less promising as an antiepileptogenic agent in laboratory studies. It has been the drug most tested in clinical trials of antiepileptogenesis, with six trials as monotherapy plus five in combination with phenobarbital in patients with traumatic brain injury, three trials in patients undergoing craniotomy, and two in patients with brain tumours.

Phenytoin dramatically decreases the incidence of seizures in the first week after traumatic brain injury (RR = 0.33, 95% CI 0.19 to 0.59, p < 0.001)[60,64,67,68] and shows a comparable effect in the study that does not separate seizures by time of occurrence (RR = 0.13, 95% CI 0.04 to 0.39, p <0.001).[5,63] As seen in table II and figure 1, there is no significant effect on late (epileptic) seizures, however (RR = 0.70, 95% CI 0.33 to 1.50, p = 0.4),[60,64,66-68] despite including the time during treatment in the evaluation. Studies evaluating the combination of phenobarbital and phenytoin have such low power that even substantial reductions in relative risk do not approach statistical significance (early seizures RR = 0, 95% CI 0 to 2.94, p = 0.2; any seizures regardless of timing RR = 0.66, 95% CI 0.21 to 2.06, p = 0.5; late seizures RR = 0.36, 95% CI 0.08 to 1.73, p = 0.3).[60,69,70]

Similar to its effects in traumatic brain injury, phenytoin has demonstrated a strong seizure-suppressive effect in the first week after craniotomy with over a 50% reduction in early seizures (RR = 0.42, 95% CI 0.25 to 0.71, p = 0.001).[72,73,89,90]

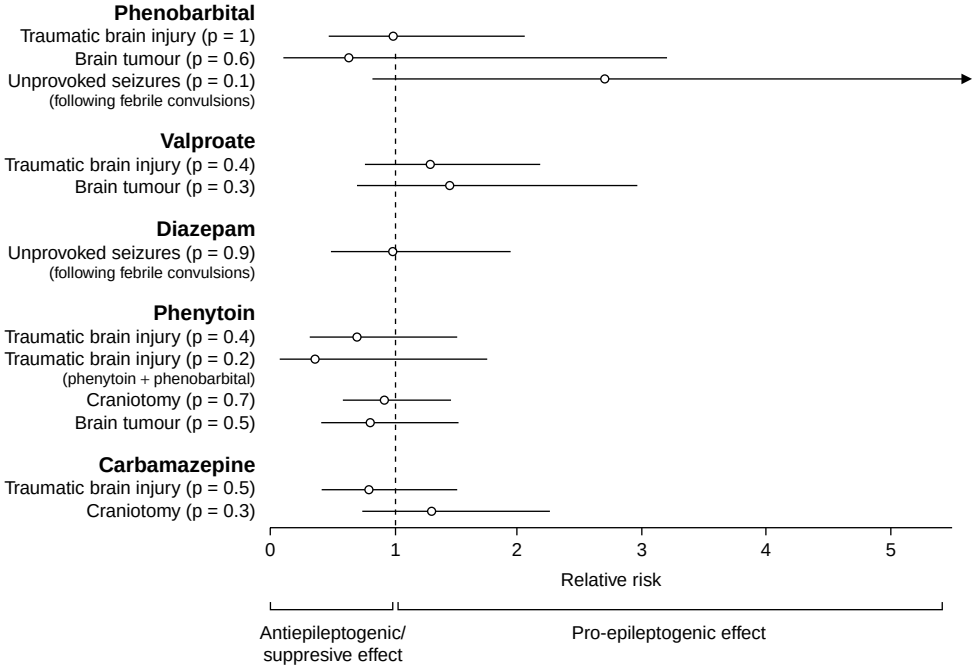

Fig. 1. Relative risk of having at least 1 epileptic seizure. The relative risk is marked by a circle and the line indicates the 95% confidence interval. Relative risks are from meta-analyses of prospective, controlled trials.

However, the effect on late seizures is neither clinically nor statistically significant (RR = 0.92, 95% CI 0.59 to 1.45, p = 0.7) despite including the time during treatment in the evaluation period.[72,73,90]

Phenytoin also had no significant effect on late seizures in two trials on patients with brain tumour (RR = 0.80, 95% CI 0.42 to 1.52, p = 0.5).[83,91]

Carbamazepine

Carbamazepine gives little suggestion of an antiepileptogenic effect in laboratory investigations. It has been evaluated in patients with craniotomy and traumatic brain injury.

The study of carbamazepine among those with traumatic brain injury shows a strong positive effect on early seizures (RR = 0.39, 95% CI 0.17 to 0.92, p = 0.03) but little effect on late seizures (RR = 0.79, 95% CI 0.42 to 1.49, p = 0.5)[71]

The craniotomy study that evaluated phenytoin and carbamazepine is unusual in that treatment was started before planned surgery so therapeutic drug concentrations were present from the time of the risk-increasing event.[72,90] With carbamazepine, there was a nonsignificant decrease in seizures during the first week after surgery (RR = 0.61, 95% CI 0.29 to 1.29, p = 0.2) and no beneficial effect on late seizures (RR = 1.30, 95% CI 0.75 to 2.25, p = 0.4).

2.3.2 Adverse Events

Medical Adverse Events

Medical adverse events reported in seizure prophylaxis trials are similar to those that occur when the same drugs are used for seizure suppression. Phenytoin, carbamazepine and phenobarbital are all associated with allergic rashes in about 5 to 15% of patients,[67,90] phenobarbital is associated with sedation, and phenytoin and valproate are associated with liver function abnormalities.[92]

Neuropsychological Effects

Neuropsychological effects have been evaluated in few studies but may be more negative than suggested by findings in epilepsy. Farwell[79,85] found IQs decreased about 7.0 points (p = 0.007) at the end of treatment for preventing recurrent febrile seizures, with a difference of 4.3 points (p = 0.09) after 6 months off treatment and a nonsignificant 3.4 points (p = 0.11) at age 8, with the latter accompanied by a significant negative effect on the Wide Range Achievement Test (WRAT) reading score. Dikmen et al.[93] found much poorer neuropsychological functioning at one month after injury in patients with severe traumatic brain injury assigned to phenytoin. Improvement in functioning was documented when prophylactic phenytoin or carbamazepine was stopped compared with randomised controls whose regimens did not change.[93,94] Valproate demonstrates no appreciable effect on neuropsychological functioning when evaluated at 1 and 6 months after traumatic brain injury.[95]

3. Conclusions

The answer to the question 'antiepileptogenic agents — how close are we?' is that we are still not very far along. Older drugs tested in humans, even those that show an excellent effect in laboratory studies, have demonstrated no antiepileptogenic effect in clinical studies, even by loose standards that combine the period of treatment with a post-treatment evaluation period. Several newer antiepileptic drugs look promising both for antiepileptogenesis and for general neuroprotection in laboratory models, but to our knowledge no clinical trial has even begun to test these compounds for antiepileptogenesis. Few antiepileptogenesis clinical trials are ongoing. A pilot study is evaluating valproate given within an hour of traumatic brain injury. The only ongoing full-scale trial we know of is evaluating magnesium sulfate for general neuroprotection including antiepileptogenesis following traumatic brain injury. That trial is taking place at our institution and results are several years off.

Where does that leave the clinician? With no drugs having a proven positive effect, with risk of seizures about 20% in most of the highest risk patients without treatment, with adverse effects — especially neurobehavioural ones — common, and with laboratory findings not translating well into humans, prescribing drugs for their antiepileptogenic potential seems foolhardy. The area of anti-

epileptogenesis is currently receiving much attention. Recently, the American Epilepsy Society devoted an entire day-long symposium to the topic and a US White House-initiated conference also focused on methods of preventing epilepsy. In the future, this may lead to more clinical trials that evaluate antiepileptogenic effects as well as behavioural and medical adverse effects so that the full range of risks and benefits can be weighed. Until some treatment shows a reliable positive effect on preventing the process of epileptogenesis, the best course to reduce the incidence of epilepsy is primary prevention of the risk-increasing events — for example, using helmets when motorcycling, bicycling, horse-back riding or snowboarding, using seat belts in automobiles, and decreasing the risk of stroke by reducing smoking and high blood pressure.[96-99]

Acknowledgements

This work was supported by grant NIN-NINDS R01NS19643.

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