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Consensus papers

Prophylaxis of the Epilepsies : should anti-epileptic drugs be used for preventing seizures after acute brain injury ?

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Abstract

In many circumstances antiepileptic drugs are used in patients who have never presented any clinical epileptic seizures. These substances are administered on the assumption of a potential risk for the patients of developing acute or delayed chronic seizures after brain injuries such as trauma, stroke, hemorrages or even neurosurgical interventions.

The aim of this paper is to propose therapeutic guidelines for the management of this prophylactic attitude in epilepsy based on basic research and clinical practice in the French community in Belgium. We will distinguish between the prevention of acute(early onset-provoked) seizures and a delayed truly post-lesional (unprovoked) epilepsy. Some therapeutic goals can be achieved under the former circumstances whereas in the latter situation we all agree for the absence of any coherent antiepileptic prophylactic behaviour.

Introduction

The epilepsies are one of the most common of the neurological disorders ; one per cent of the world population is considered as having epilepsy, about 50 millions persons worldwide.

An epilepsy, or an "epileptic syndrome", is defined as a chronic disorder characterized by recurrent unprovoked seizures of a specific type and/or age of onset, with a suspected aetiology, EEG pattern and particular prognosis or antiepileptic drug sensitivity. When such a disease is recognized, it can benefit from various treatments including at first line antiepileptic drugs, but also surgery, neurostimulation and psychotherapy.

Epilepsy is a group of essentially excitable disorders of brain function revealed at the EEG level by episodes of gross electrical disturbances. It is noteworthy that epilepsy can be caused by virtually any major category of serious disease or disorder of humans. It can result from a subtle genetic mutation, congenital malformations, infections, tumours, vascular and degenerative diseseases, or any other injury including brain trauma or even neurosurgical procedures. In front of such chronic and very often disabling illnesses, it has been dreamed several times to prevent the occurrence of an epileptic disorder when such a particular brain injury occurs. This has been called : "prohylaxis of epilepsy". Unfortunately, if one knows the list of the various brain injuries with potential epileptogenic traits, the knowledge of the exact basic neurobiological processes which lead from the initial lesion to the developpement of either acute seizures or delayed chronic post lesional epilepsy remain meager. Accordingly, besides data arising from recent information from basic research and clinical practice as reported in various epidemiological studies, there is actually no real rational for a systematic prophylactic attitude in epilepsy.

In this paper, we will review the fundamental risk factors for developing a post-lesional epilepsy as mentioned by research on the basic mechanisms of the epilepsies, then the main data from epidemiolgical studies, and finally the global attitude we propose in this field, according to actual current clinical practice.

Risk factors for epileptogenesis

Epileptogenesis is the transformation of an area of the brain to a long-lasting state in which seizures occur spontaneously or are easily triggered.

Until now our therapeutic attitude in epilepsy is the use of anticonvulsant drugs to reduce seizure expression. It has long been recognized however that a better approach would be to employ molecules capable of preventing the induction process of epilepsy. Hence antiepileptogenic drugs could be dinstinguished from traditional anticonvulsants.

The mechanisms underlying these epileptogenic processes are thought to be diverse, ranging from genetic defects to complex changes secondary to traumatic injury. In principle, any changes that alter the gross equilibrium between excitation over

Table 1

Characteristics of experimental acute epileptogenesis(from ref 2)

Acute epileptogenesis occurs in anatomical areas often involved in certain types of chronic epilepsy.
Acute epileptogenesis can be induced *in vivo* or *in vitro* with a variety of convulsant drugs, altered ion concentrations, or repeated stimulus trains.
The time course ranges from minutes to hours, but each type of eperimental model has a typical, sometimes relatively narrow, range.
The brief time frame suggests that some of the mechanisms hypothesized to underlie chronic epileptogenesis (e.g., extensive recurrent sprouting or gliosis) do not underlie acute epileptogenesis.
Acute epileptogenesis may be reversible.
The antiepileptogenic pharmacologic profile parallels that of certain other types of acute neuroplasticity (e.g., long term potentiation) as well as ch ronic epileptogenesis. NMDA antagonists block acute epileptogenesis but are less effective against the expression of epileptiform activity. In addition, mGluR activity may also be involved, directly or indirectly.
Development affects both the induction and expression of acute epileptogenesis.
In the *in vitro* models of SE, epileptogenesis can be progressive even after the withdrawal of an epileptogenic agent or stimulus.
In models of SE, the anticonvulsant pharmacologic profile can change over the course of acute epileptogenic agents or stimuli.
In the *in vitro* models of SE, cell loss can occur acutely, epileptiform activity may be necessary for the damage, and activation of both NMDA and non-NMDA glutamatergic receptors may play a role in this process.

The studies reviewed in this chapter (ref 2) have revealed characteristics of acute or rapid epileptogenesis that appear to be common across many experimental systems. These may provide clues about the underlying mechanisms of acute epileptognesis and status epilepticus activity (Note that the last three items on this list relate specifically to characteristics of epileptogenic changes reported in models of status epilepticus).

NMDA, N-methyl-D-aspartate ; SE, status epilepticus.

(From ref. 2).

inhibition is a potential epileptogenic mechanism. Furthemore, experimental evidences indicates that anticonvulsant drugs and antiepileptogenic agents are not necessarily identical.

Clearly, here, we will focus on epileptic disorders that result from exogenous epileptogenic insults (i.e. : non genetic) and then divide these acquired mechanisms into acute/provoked and delayed/ unprovoked subgroups.

WHAT CAN WE LEARN FROM EXPERIMENTAL STUDIES ?

Most basic studies (1) of epileptogenesis have indeed concentrated on either genetic or chronic morphologic changes that are associated with clear clinical correlates. However, over the past two decades, studies in experimental animals have provided evidence that epileptogenesis can also be an acute process. That means that relatively long lasting hyperexcitability can result from events that occur over the course of minutes, hours, or days, rather than weeks, months, or years.

One of the first points to take in account is the site of the lesion.

Acute epileptogenesis can be rapidly induced *in vivo* in many brain areas known to be involved in chronic epilepsy. These include the hippocampus, amygdala and neocortex. Remarkably, *in vitro* studies have shown that slices of the same areas can also undergo epileptogenesis (1). Induction methods range from repeated stimulus trains, brief periods of exposure to toxins (kainic acid, picrotoxin) or exposure to altered extracellular ions concentrations. Changes in synaptic efficacy, altered receptor expression, cell loss and presynatic terminal hyperexcitability are potential mechanisms of this acute epileptogenesis. This suggests that epileptogenesis can occur in the absence of dramatic anatomic changes. The table 1 (2) summarizes the principal characteristics of experimental acute epileptogenesis. In principle, these characteristics could constitute some basic indications for appropriate anti epileptiogenic attitude. Indeed a cascade of morphologic and biologic changes in the injured area over minutes, hours, days, monthes and even years can potentially lead to hyperexcitability and epileptogenesis. This “latent” period between injury and the first unprovoked seizures, may offer a therapeutic window for the prevention of epileptogenesis. This phenomenon refered to as “neuroprotection” in epilepsy. Today, a significant amount of data arised from experimental studies, showing some new concepts in biological phenomena associated with this latent period and even first exciting results in the parmacological prophylaxis of experimental epilepsy (3, 4). We have to recognize, however that in the human being, little is known concerning the basic mechanisms of this crucial latent period and administration of anticonvulant drugs following acute brain insults has thusfar failed to prevent late epilepsy.

EPIDEMIOLOGICAL CLINICAL STUDIES

In clinical practice several attempts have been published to determine the risk factors for developing a late epilepsy after various initial brain injuries.

The most significant risk factors are summarized in table 2 (5, 6, 7, 8).

As shown, significant brain damage accompanied by some early neurological signs in cortical and sub-cortical region of the brain in young

Table 2

Risk factors of post traumatic epilepsy

Significant initial brain damages
Hemorrhage
Depression fracture
Diffuse contusion
Missile injuries
Early neurological signs
Focal deficits
Loss of consciousness (> 24 hours) or GCS = 3-8
Amnesia (> 24 hours)
Immediate or early seizures (< 24 hours)
Site of the lesion
Cortical-sub-cortical
Frontal
Secondary
Age (young or older)
Alcohol abuse

See text for comments (From ref 5, 6, 7 and 8).

people constitutes the prototypic clinical situation where a true post lesional epilepsy could arise, at high risk, in a period ranging from 6 weeks to 2 years after the initial injury. Whether or not a genetic predisposition is needed to increase the risk is still a matter of debate.

Brain trauma

Englander *et al.* (8) has recently showed, in a prospective multicenter investigation, that the highest cumulative probability for late posttraumatic seizures include biparietal contusions (66%), dural penetration with bone and metal fragments (62.5%), multiple intracranial operations (36.5%), multiple subcortical contusions (33.4%), subdural haematoma with evacuation (27.8%), midline shift greater than 5mm (25.8%), or multiple or bilateral cortical contusions (25%). This study confirms the results of previous studies where the risk is highly correlated to the severity of the trauma (1.5% for mild to 417% for severe trauma) and the type of trauma (risk to 53% if projectile related injury).

Spontaneous supratentorial intracranial haemorrhage(ICH)

Among a cohort of 761 patients with ICH (9) 57 had one or more seizures, the 30-day actuarial risk of a post ICH seizures was 8.1%, i.e. much lower than prevoiusly thought. Lobar location and small volume of ICH were independent predictors of immediate (within 24 of ICH) seizure. Early seizures (within 30 days of ICH) was associated with lobar location and neurological complications mainly rebleeding.

Claassen *et al.* (10) prospectively analyzed 247 of 431 patients with subarachnoid hemorrage (SAH) treated over a period of 5 years who were alive with follow-up at 12 months. Epilepsy was defined as two or more unprovoked seizures after hospital discharge. New-onset epilepsy occurred in 7% (n = 17) of patients ; an additional 4% (n = 10) had only one seizure after discharge. Independent predictors of epilepsy included subdural hematoma and cerebral infarction. Unlike those without seizures, patients who developed epilepsy failed to experience functional recovery on the modified Rankin Scale(mRS) between 3 and 12 months after SAH. After 12 months epilepsy was independently associated with severe disability, increased instrumental disability, reduced quality of life, and an increased state of anxiety. Epilepsy was not associated with cognitive impairment, depression. Finally their findings indicate that focal pathology, rather than diffuse injury from hemorrhage, is the principal cause of epilepsy after SAH.

Stroke

Stroke is one of the most frequent causes of seizures in adulthood. Subcortical infarcts have been associated with post-stroke epileptic seizures, although less frequently than cortical ischaemia. Bentes *et al.* (11) for instance studied 113 patients from a hospital stroke registry. The patients had subcortical non-lacunar infarcts and at least 1 year of follow-up. Only 4 patients (3.5%) with striatocapsular infarcts suffered an epileptic seizure. Two seizures occurred within the first 24 h, 1 within the first month and 1 within the first year of stroke onset. Emboligenic cardiac conditions were significantly more common in patients with seizures. Subsequently to subcortical infarct, epileptic seizures are infrequent, tend to occur early after stroke and have a very low 1-year recurrence risk.

In the course of a recent retrospective processed treatment of the patients Alajbegovic *et al.* (12) reviewed 7001 patients with the various types and subtypes of cardiovascular insult. The incidence of epileptic seizure changed from 0.65% (1994) up to 3.14% (1998). 111 patients exhibited late epileptic seizures, and 56 patients had early epileptic seizures.

In a recent study, among 1000 consecutive patients, Cheung *et al.* (13) showed that thirty-four patients (3.4%) developed seizures within one year after acute stroke. Univariate analysis revealed that male gender, age greater than 65 years, total anterior circulation infarction, partial anterior circulation infarction, cortical location and large lesion were significantly associated with post-stroke seizures while multivariate analysis showed that only male gender (adjusted OR 3.21, $p < 0.01$) and cortical location (adjusted OR 3.83, $p < 0.05$) were significant independent risk factors. Fifty-six percent of early seizures were partial type whereas 72% of late seizures were generalized tonic-clonic type of undetermined onset. Seizures occurred in 3.4% of

patients within one year after the onset of stroke. This percentage of seizure occurrence and associated risk factors were similar to previous studies.

In young adults, the picture is somwhat different. For instance, Lamy *et al.* (14). demonstrated that fourteen of the 581 patients (2.4%) developed early seizures, 71% of which occurred within the first 24 hours. Rankin scale > or = 3 and cortical involvement were independently associated with early seizures. Late seizures occurred only in patients with hemispheric stroke (n = 20). The risk of first late seizure was 3.1% within 1 year and 5.5% within 3 years. The mean delay between stroke and first late seizure was 12.9 months. Late seizures were associated with early seizure, cortical signs, and size of infarct superior to one-half hemisphere. Interestingly, eleven of the 20 patients with late seizure experienced recurrences on antiepileptic drug treatment. Most of them were seizure free at the end of the follow-up. Therefore epilepsy rarely seems to be a major problem in young cryptogenic ischemic stroke survivors. Early seizures are associated with stroke disability and cortical involvement. Early seizures, cortical signs, and large infarct are independent risk factors for late seizures.

In the elderly, Silverman *et al.* (15) has already elegantly reviewed the question of post stroke seizures. They insisted on the fact that stroke is finally the most common cause of seizures during this period of age whileseizures are among the most common neurologic sequelae of stroke. About 10% of all stroke patients experience seizures, from stroke onset until several years later. Their review discusses current understanding of the epidemiology, pathogenesis, classification, clinical manifestations, diagnostic studies, differential diagnosis, and management issues of seizures associated with various cerebrovascular lesions, with a focus on anticonvulsant use in the elderly.

More recently, Granger *et al. (*16) used a cohort of 341 subjects aged over 60 years, who experienced their first epileptic seizure. Forty one per cent of the seizures were generalized and 59% were partial. Status epilepticus occurred in 8%. The EEG recording was contributive to diagnosis or helpful for localizing the epileptic focus in 55% of the patients. Normal brain imaging was observed in 40 p.cent of the patients. The main etiology was cerebrovascular disease, acute stroke, or more often postvascular epilepsy.

On the other hand, Naylor *et al.* (17) in a prospective audit showed that eight patients only (0.8%) suffered a seizure (three bilateral) < 30 days following 949 carotid endarterectomies (CEAs) Seizures were not associated with age, gender or presentation.

Therefore there exists some rational in favour of a prophylactic attitude in the case of post stroke or even post ischemic epilepsies.

Tumors

As recently revisited by Schaller and Ruegg (18), seizures affect approximately 50% of patients with primary and metastatic brain tumors. Partial seizures have the highest incidence, followed by secondarily generalized, seizures depending on histologic subtype, location, and tumor extent. The underlying pathophysiologic mechanisms of tumor-associated seizures are poorly understood and include theories of altered peritumoral aminoacids, regional metabolism, pH, neuronal or glial enzyme and protein expression, as well as immunologic activity. Involvement of a changed distribution and function of N-methyl-d-aspartate subclass of glutamate receptors has also been suggested. The often unpredictable responses to seizures after surgical tumor removal add substantial evidence to the fact that multiple factors are involved. The therapy of tumor-related seizures is far from perfect. Several factors contribute to these treatment difficulties, such as tumor growth and drug interactions ; however, one of the main reasons for poor seizure control may result from the insufficient or even absent influence of the currently available antiepileptic drugs (AEDs) on most of the pathophysiologic mechanisms of tumor-related seizures.

In cancer patients without primary brain tumors or brain metastasis, epileptic seizures may occur due to metabolic or toxic causes, or due to infections. Oberndorfer *et al.* (19) performed a retrospective analysis of the occurrence of seizures in patients with primary brain tumors, patients with cerebral metastases and in cancer patients without brain tumors. Patients with low grade gliomas, such as astrocytoma WHO I + II (69%), oligodendroglioma WHO II (50%), and mixed glioma WHO II-III (56%) were more likely to have seizures than patients with anaplastic glioma WHO III (44%), glioblastoma WHO IV (48%) or meningeoma (45%). In patients with brain metastasis, melanoma (67%), cancer of the lung (29%), and gastrointestinal tumors (21%) were the primaries with the highest frequency of seizures. In cancer patients without brain metastases or primary brain tumors, seizures occurred in 4%.

In children, Shuper *et al.* (20) attempted to correlate the onset of epilepsy with the disease stage with brain tumors through treatment and follow-up in their oncologic department. The study sample consisted of a heterogenous group of 219 children who were aged 6 months to 11 years, manifested brain tumors. The overall rate of epilepsy was 14.6%, which rose to 38% in those with cortical tumors. Two major causes of epilepsy were evident : tumor-related and treatment-related. The first group could be further divided into epilepsy starting at or before diagnosis of brain tumor, epilepsy associated with tumor progression, and epilepsy starting at end-stage disease. The second group

could be divided into epilepsy caused by radiation damage to the brain and epilepsy related to another postoperative state. The data emphasize the significance of striving for complete tumor resection and the potential damage from the use of radiotherapy to the brain. The authors suggest that a change in local neurotransmitter balance may be the mechanism underlying tumor-related epilepsy.

Luyken *et al.* (21) attempted to determine which histologic spectrum and clinical characteristics of patients with neuroepithelial tumors are associated with drug-resistant epilepsy and analyzed clinical data and treatment related to seizure outcome and survival. Data were analyzed from 207 consecutive patients with intractable epilepsy who between had resection of supratentorial, neuroepithelial tumors. Histologic examination revealed 154 classic epilepsy-associated tumors (ganglioglioma, dysembryoplastic neuroepithelial tumor, pleomorphic xanthoastrocytoma, and pilocytic astrocytomas) and 53 others. The following factors were associated with improved seizure outcome : short duration of epilepsy before surgery, single EEG focus, absence of additional hippocampal sclerosis or cortical dysplasia, transsylvian surgical approach, other than for astrocytomas, and complete tumor resection. These authors concluded that tumors associated with long-term epilepsy should be removed early for two different reasons : high rate of seizure freedom and rare but potential risk of malignant tumor progression. Incidently, the unexpected long survival of some astrocytomas is intriguing and should be investigated by using immunohistochemistry and molecular biology.

Obviously this list remains uncomplete. Other causes like a simple neurosurgical procedure should also be mentioned. These above reviewed risk factors in various forms of epilepsies however clearly indicate the diversity of the patophysiological mechanisms of these diseases and accordingly make illusive the possibility of any single or simple appropriate prophylactic therapeutic attitude in epilepsy.

In summary, early provoked seizures seem to be produced by mechanisms completely different from delayed seizures. Early seizures are often secondary to acute metabolic and cardiovascular changes and most of time have a generalized tonic-clonic symptomatology.
On the other hand, delayed unprovoked seizures appear after a “silent” period, during which epileptogenesis is ongoing. Most of the time seizures have focal onset symptoms with or without secondary generalization.

Prophylaxys of the epilepsies according to some epidemiolgical studies

Keeping in mind all the above described basic mechanisms and risk factors, how can one define any therapeutic attitude or, even better, any prophylactic approach acting on a specific mechanism implicated in a particular post-lesional epilepsy ? At the present time, a true prophylactic treatment of epilepsy is not yet available in humans. However, antiepileptic drugs are useful to avoid acute seizures in most situations and should be prescribed during this acute period.

Most of the studies used first generation antiepileptic drugs (Phenobarbital, Phenytoïne, Valproate or Carbamazepine). In animals, promising results were published with new AEDs.

It is virtually impossible to review or even summarize the clinical papers attempting to answer the problem. There certainly exists among these studies a very large diversity in patient selection, the type of the explored epilepsy as well as the drugs used.

Reviewing the data, in view of defining a therapeutic attitude, it is clear that we have to distinguish between preventing the risks for “acute or immediate seizures or epilepsy” (within minutes or hours) or “early seizures or epilepsy” (within 24-48 hours) and “late epilepsy” (after weeks) following any initial brain injury.

Note that during the following discussion, the question of treating patients exhibiting early or late seizures as part of the clinical picture is not taken to in consideration as they are considered as having a specific form of epilepsy and therefore have to be adequately treated.

Preventing post lesional late epilepsy

With some exception like a study published by Murri *et al.* in 1992 (22) who suggested a real prophylactic effect of phenobarbital on posttraumatic seizures, most of the clinical trials failed to prove any prophylactic influence of the conventional anticonvulsants on postlesional late epilepsy. As early as in 1994, Dieter Janz (23) wrote : “Regarding the prevention of seizures, routine prophylactic treatment with antiepileptic drugs is not appropriate, since the benefits do not outweight the risks”. Later on a randomized, blinded, placebo-controlled trial of divalproex sodium prophylaxis in adults with newly diagnosed brain tumors, rejected the hypothesis that anticonvulsant prophylaxis provides a reduction in the frequency of occurence of a first seizure (24).

A japanese cooperative multicentric study (25) on posttraumatic epilepsy (PTE)confirmed that anticonvulsant treatment after head injury was unlikely to have a prophylactic effect on the development of PTE. Similarly, one of the first meta-analysis in the field (26) reviewing controlled trials including up to 2036 patients confirmed insufficient evidence available, at least in 1998, to establish the net benefit of prophylactic treatment at any time after acute traumatic head injury.

The subcommittee of the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation presented in 1998 (27) the following recommendations : 1) Prophylactic use of phenytoin (PHT), carbamazepine (CBZ), sodium valproate (VPA), or phenobarbital (PB) is not recommended for preventing late post traumatic seizures, defined as seizures that occur after 1 week of injury, in the patient in whom there has been no history of seizures following a nonpenetrating traumatic brain injury (TBI). 2) It is recommended as a treatment option that PHT, PB, and CBZ may be used to prevent early PTS in patients at high risk for seizures following TBI. 3) Prophylactic use of PHT, CBZ, VPA, or PB is not recommended for preventing late PTS following penetrating TBI.

Another meta-anlysis (28) has been more recently (2001)conducted to synthesize evidence concerning the effect of antiepileptic drugs (AEDs) for seizure prevention and to contrast their effectiveness for provoked versus unprovoked seizures. Forty-seven trials have been reviewed evaluating seven different drugs or combinations for preventing seizures associated with fever, alcohol, malaria, perinatal asphyxia, contrast media, tumors, craniotomy, and traumatic brain injury. The author concluded that effectiveness was demonstrated for provoked (acute, symptomatic) seizures whereas for unprovoked (epileptic) seizures, no drug has been shown to be effective.

To determine the effects of prophylactic antiepileptic agents for acute traumatic head injury Schierhout and Roberts (29, 30) searched in the Cochrane Injuries Group specialised register, Medline and the registers of the Cochrane Stroke Group and Cochrane Epilepsy Group. They contacted pharmaceutical companies who manufacture anti-epileptic agents, the National Institute of Neurological Disorders and Stroke, Epilepsy Division, and the National Institute of Health, USA. Their conclusions were that prophylactic use of antiepileptics is effective in reducing early seizures, but that there is no evidence that treatment with prophylactic anti-epileptics reduces the occurrence of late seizures, or has any effect on death and neurological disability. Insufficient evidence is available to establish the net benefit of prophylactic treatment at any time after injury. De Santis *et al.* (31) showed that PHT, given at dosages producing serum concentrations within the target range, failed to prevent early postoperative seizures in patients treated with concomitant AEDs. Therefore, prophylactic administration of PHT cannot be recommended in these patients.

At the occasion of the first congress of the Spanish League against Epilepsy, Garibi (32) reviewed the use of antiepileptic drugs for preventing postoperative and posttraumatic seizures. Two specific causes of epilepsy are particularly relevant to neurosurgical practice ; postoperative and posttraumatic epilepsy. His conclusion was again that no treatments has yet been shown to be effective in preventing the development of epileptic seizures.

Finally, more recently Chang and Lowenstein (33) reviewed the evidence regarding antiepileptic drug (AED) prophylaxis in patients with severe traumatic brain injury (TBI) in order to make practical recommendations. They identified relevant studies by searching multiple databases and reviewing reference lists of other sources. They included studies that prospectively compared posttraumatic seizure rates in patients given AED prophylaxis versus controls. They concluded that for adult patients with severe TBI, prophylaxis with phenytoin is effective in decreasing the risk of early post-traumatic seizures. AED prophylaxis however is probably not effective in decreasing the risk of late post-traumatic seizures. The same conclusions were reached in the case of epilepsy associated with brain tumours (34) or in brain ischemia (35).

Preventing post lesional acute or early epilepsy

As already mentionned in some reviewed studies above, anticonvulsant seem poorly effective in preventing late post traumatic post lesional epilepsy. Hence, it could be approriate to treat patients exhibiting a high risk of seizures, among which a single clinical attack (see table 2) in the first minutes (acute, immediate seizures or epilepsy) up to 24-48 hours (early seizures or epilepsy) for a certain period of time in order to avoid the occurrence or an immediate relapse of seizure activity. Haltiner *et al.* (36) tried to determine if the use of phenytoin to prevent early posttraumatic seizures following head injury was associated with significant adverse side effects and also to determine if the reduction in early posttraumatic seizures after phenytoin administration was associated with a change in mortality rates in head-injured patients. The authors performed a secondary analysis of the data obtained in a prospective double-blind placebo-controlled study of 404 patients who were randomly assigned to receive phenytoin or placebo for the prevention of early and late posttraumatic seizures. The results of this study indicate that the incidence of early posttraumatic seizure can be effectively reduced by prophylactic administration of phenytoin for 1 or 2 weeks without a significant increase in drug-related side effects. Reduction in posttraumatic seizures during the first week, however, was not associated with a reduction in the mortality rate.

This has also been the conclusion of the Brain Trauma Foundation in 2000 (37) : “Phenytoin and carbamazepine have been shown to reduce the incidence of early PTS. Valproate may also have a comparable effect to phenytoin on reducing early post traumatic seizures but may also be associated

with a higher mortality. It is, therefore, an option to use phenytoin or carbamazepine to prevent the occurrence of seizures in high-risk patients during the first week following head injury".

Phenytoin and carbamazepine seem therefore effective in preventing early, but not late, posttraumatic seizures. In a recent study the Temkin *et al.* (38) compared the safety and effectiveness of valproate versus phenytoin for prevention of seizures following traumatic brain injury. Valproate therapy shows no benefit over short-term phenytoin therapy for prevention of early seizures and neither treatment prevents late seizures. There was a trend towards a higher mortality rate among valproate-treated patients. The lack of additional benefit and the potentially higher mortality rate suggest that valproate should not be routinely used for the prevention of posttraumatic seizures.

When deciding to prophylactically administer an antiepileptic drug to a patient without seizure history, one has to weight the possible deleterious side effects of the drugs against a possible prophylactic benefit. A comparative study of phenytoin and carbamazepine in patients recovering from brain trauma has been conducted by Smith *et al.* (39) to compare the effects of prophylactic anticonvulsant use of phenytoin and carbamazepine on the cognitive and emotional status of the patient. Their conclusions was that both phenytoin and carbamazepine seem to have negative effects on cognitive performance, particularly on tasks with significant motor and speed components. Practice effects were noted and may account for much of the improvement when patients stopped taking the drugs. Overall effects of the drugs were small and of limited clinical significance, but differences among subjects were noted that may affect selection of a particular drug for the individual patient.

Conclusion : **propositions for a** "**prophylactic**" **approach in epilepsy**

Comparing our own routine clinical experience among different centers of the French Community of Belgium (although not yet documented by an approriate study) with the above summarised data from the literature, we can propose the following as an appropriate prophylactic approach in front of an established risk of any post lesional epilepsy or delayed unprovoked seizures.

1. The first step in preventing epilepsy is of course to avoid as much as possible the causes or risk factors.

2. The recommended therapeutic strategy is first to evaluate the risk factors on the basis of a careful established list presented in table 2.

3. In the absence of such risk factor we do not recommend to treat patient with any anticonvulsant drug, especially in view of the ratio between prophylactic efficacy versus adverse events and even cost of the drugs.

4. In the presence of one or more risk factors, including acute or early seizures, we propose to treat the patients with an appropriate dose of one single classic antiepileptic drug (AED), with proven efficacy in partial seizures as reported in a previous guideline(40), but for a short period of time ranging from 1 week to maximum 3 months, if no relapse of seizure activity occurs.

Today no information is available concerning the use of new AEDS having in general the best achievable tolerability. We do not see any reasons to avoid their use since they often share some identical fundamental mechanisms of action with the calssic AED's.

This proposal does not recommend to administer AEDs to patients undergoing a regular neurosurgical procedure for which no real risk factor has been identified.

Finally, we must insist on the importance of new advances in the knowledge of the fundamental mechanisms responsible for the developement of postlesional epilepsy in the human brain in order to identify the true molecular early targets (lipid peroxydation inhibitors, antioxydants, NMDA receptor blockers, drugs modulating apoptosis etc…) for a true pharmacological prophylaxis of postlesional epilepsies. There is a need to design clinical studies with the goal of demonstrating their antiepileptogenic and/or neuroprotective activity at different ages in life. New and future therapeutic modalities may then offer additional preventive options.

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