Do anticonvulsants alter the natural course of epilepsy?

Treatment should be started as early as possible

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This is the seventeenth in a series of articles examining some of the difficult decisions that arise in medicine

Throughout this century the pharmacological treatment of epilepsy has been based on the Jacksonian concept, reinforced after Berger's discovery of the electroencephalograph, that seizures represent neuronal discharges that need to be suppressed by antiepileptic drugs. According to this view, when antiepileptic drugs are withdrawn seizures may be expected to recur unless the seizure disorder has gone into spontaneous remission, which apparently happens in a high percentage of cases.¹

A more recent view, which has some neglected historical roots,² suggests that antiepileptic drugs may also influence the natural history of epilepsy, that epilepsy should be viewed as a process that has the potential to develop into an intractable disorder, and that early effective treatment may reduce this risk of chronicity.^{3,4}

Clinical studies

Epilepsy used to be thought of as a chronic disorder in most patients, but recent community and hospital based studies of newly diagnosed patients have shown that only 20-30% of patients develop intractable epilepsy.^{3,4} Is this intractability inevitable because we do not have powerful enough drugs to suppress more "severe" forms of epilepsy or could some of it be avoided by early treatment to prevent the escalation of the process of epilepsy into a chronic disorder?

Several studies have confirmed Gower's observation² that the longer the history of epilepsy the worse the longer term prognosis.^{3,4} Only Feksi *et al* in East Africa, based on a retrospective analysis of poorly educated patients with a mean duration of epilepsy of seven years, did not agree.⁵ Many factors can adversely affect prognosis in epilepsy including partial or mixed seizure types (compared with tonic-clonic seizures), symptomatic epilepsy, clinical or computed tomographic evidence of cerebral disease, intellectual handicap, psychiatric illness, personality change, or social problems. In recent long term prospective studies of 241 adults and 167 children with newly diagnosed epilepsy who were treated with one drug the most important influence on prognosis was the number of seizures before starting treatment; the more seizures the worse the prognosis (figure).⁶ Number of seizures was a more important determinant of prognosis than frequency of seizures before treatment.

An important difficulty in this debate is that we do not know the natural course of untreated epilepsy. For ethical reasons it would be difficult to study this prospectively, but in a retrospective study of 183 patients presenting to a neurological outpatient department with between two and five untreated tonic-clonic seizures Elwes *et al* found a declining interval between seizures in most patients.⁷ This finding is in keeping with an escalating process of epilepsy in the early stages.

Patients with a single unprovoked seizure may also benefit from treatment, although they are currently excluded from the definition of epilepsy and not

usually treated. Two recent controlled trials have shown a significant improvement in medium term outcome with immediate treatment compared with either placebo or delayed treatment in patients presenting with single seizures.^{8,9} Furthermore, in patients having antiepileptic drugs withdrawn slowly after prolonged remission the most important determinant of a good outcome was the length of remission—the longer the remission the greater the chance of success.¹

Percentage of patients achieving one year remission according to number of seizures before treatment. Data obtained from study of 241 adults with newly diagnosed epilepsy treated with one drug

Experimental studies

The kindling model of epilepsy provides some experimental support for the view that epilepsy should be seen as a process. In various animal species repeated subthreshold electrical or chemical stimuli can culminate in a kindled seizure, and this in turn can sometimes lead to recurrent spontaneous seizures. Seizures induced by kindling can induce neuronal loss in some limbic pathways, including the dentate gyrus, accompanied by sprouting and permanent reorganisation of the synaptic connections of the mossy fibre pathway. Furthermore, there is now evidence that brief pharmacological intervention can alter the long lasting effects of seizures, reduce susceptibility to the development of epilepsy, and alter the prognosis of experimental epileptic syndromes induced by kindling or kainic acid.¹⁰

Conclusion

Much evidence exists to support the view that epilepsy is a process that should be treated as early and effectively as possible to try to prevent the development of chronic, intractable epilepsy. This does not exclude the possibility of spontaneous remission in some patients, especially with some childhood epilepsy syndromes, and anticonvulsant drugs may help this process. Further studies are indicated since any reduction in the incidence of chronic epilepsy, with its many complications and high economic costs, would be a major achievement in the treatment of epilepsy.

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Case for early treatment is not established

David Chadwick

The most important question in epilepsy is whether antiepileptic drugs not only reduce susceptibility to seizures in someone with epilepsy but also modify the natural course of the condition. The concept of a process of epileptogenesis is strongly grounded in the large volume of work on the kindling model of epilepsy¹ and is supported by some circumstantial clinical evidence. However, I believe that the clinical evidence weighs against early treatment with antiepileptic drugs affecting natural course at a practical level.

Clinical evidence

Epilepsy is a group of disorders in which seizures occur and not a homogeneous disease entity. The response to antiepileptic drugs may therefore differ. The issue of heterogeneity can be partly addressed by looking at the prognosis for epilepsy syndromes and the likelihood of their being influenced by antiepileptic drugs. One clear cut children's epilepsy syndrome is that of benign rolandic epilepsy, in which focal motor seizures, usually affecting the face, throat, and arm, occur during sleep in children between the ages of 7 and 12. Seizures stop by mid-adolescence,² and many paediatricians no longer give such children antiepileptic drugs since the outcome seems to be entirely benign whether or not treatment is given.

A rather different picture arises in juvenile myoclonic epilepsy. This syndrome develops in adolescence. Patients experience early morning myoclonus and tonic-clonic seizures and have generalised spike waves in the electroencephalogram. The syndrome often responds well to sodium valproate, but there is a high probability of relapse if the drugs are withdrawn irrespective of how long the patient has been free of seizures during treatment.³ Prolonged treatment does not seem to influence the likelihood of long term cure.

Few studies have addressed the issue of which factors determine longer term prognosis. Shafer *et al* looked at factors that predicted achieving a five year seizure remission with and without treatment.⁴ Developing epilepsy before the age of 16, having no evidence of brain damage early in life or a cause for epilepsy, never having experienced tonic-clonic seizures, and not having spike wave abnormalities in the electroencephalogram were all favourable. It is difficult to see how any of these prognostic factors might be influenced by early treatment.

One difficulty in assessing the impact of drugs on the natural course of epilepsy is that people with untreated epilepsy are rarely studied. Recently Keranen and Riekkinen identified 33 patients in a community based population who had never been treated.⁵ Though this is a selected population, the remission rate was 52% at

20 years, comparing reasonably with outcomes in treated populations.⁶

Another approach is to examine the effect of antiepileptic drugs in underdeveloped countries, where treatment is often delayed. In studies of antiepileptic treatment in 302 patients in Kenya⁷ and 192 patients in Ecuador⁸ most of the patients had experienced seizures for many years without any treatment. If antiepileptic drugs affected the natural course this group of patients would be expected to do significantly worse than patients presenting with a recent history of epilepsy in developed countries. In fact, six month remission rates were similar to those that would be expected with earlier treatment.

Evidence from randomised trials

The evidence from clinical trials and surveys, however, is circumstantial and retrospective. Randomised clinical trials have provided stronger evidence. Temkin *et al* looked at the proportion of patients treated with placebo or phenytoin (in doses to obtain optimal blood concentrations) who had seizures after head injury.⁹ More patients receiving phenytoin had seizures than those receiving placebo. More recently, an Italian multicentre study¹¹ randomised 400 patients with a first seizure to treatment or no treatment and looked at both time to first seizure after randomisation and time to obtaining a remission of six or more months.¹⁰ Patients randomised to treatment after a first seizure had about half the risk of a further seizure by two years. So far, however, there is no evidence of any difference between the two groups in terms of time to a remission. Thus, none of the available clinical trials comparing early treatment with deferred treatment seemed to show any great benefit to longer term outcomes.

Practical considerations

Early treatment for epilepsy raises considerable practical problems. Firstly, if the process of kindling occurs in humans there is good evidence from animal models that the effects of antiepileptic drugs on kindling are greater the earlier in the process they are given. This would therefore raise difficult issues about identifying people for treatment long before perhaps even this first seizure had occurred. Secondly, until several events have occurred it is often difficult for clinicians to be certain that they were seizures and they are therefore unwilling to prescribe antiepileptic drugs, which might need to be taken for at least one or two years.

The final practical issue is that of patient compliance. This contributes significantly to the failure of antiepileptic treatment. It is likely to be much more

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