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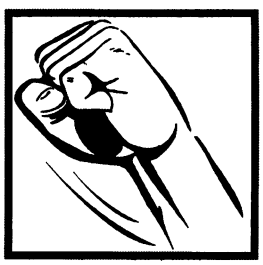
Case for early treatment is not established

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 epilepsy[1] 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 The syndrome often responds well to sodium valproate, but there is a high probability of relapse if the drugs are withdrawn irrespective of how long the patient has been free of seizures during treatment.[3] Prolonged treatment does not seem to influence the likelihood of long term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 Keyna[7] and 192 patients in Ecuador[8] 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 study[11] 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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Commentary: reliable data are not yet available

Epilepsy is a syndrome of varying aetiology. Although drugs do not seem to be effective in head injured patients, the natural course of epilepsy in these patients seems unlikely to be the same as that in a person with no identifiable cause. The preliminary data on treatment after a first seizure are encouraging but far from definitive, and it is in this area that most effort must be concentrated. The social implications of diagnosing epilepsy after the first seizure are substantial, making it all the more important that reliable data are obtained. Though the widespread use of anticonvulsant drugs prevents a comprehensive study on the natural course of epilepsy in all its forms, the effect of treating or not treating the first seizure should be thoroughly investigated.—PETER C RUBIN, *professor of therapeutics, University of Nottingham*

difficult to encourage patient compliance after one or two seizures than after a clear pattern of epilepsy has been established. Treating epilepsy before the first seizure presents even more difficulties.

Conclusion

The decision to start antiepileptic drugs is difficult for any patient. Currently, we are unable to offer patients enough information to make this decision easy or to encourage compliance with early treatment. The estimates of risks of a second seizure after the first vary widely,[11] and even less information is available about the risk of third seizures after a second. We need studies that allow a precise estimate of the differences in short term recurrence of seizures with and without treatment as well as an estimate of how different the chance of long term cure (remission without antiepileptic drug treatment) is if treatment is started early rather than later. These estimates would need to be set against information about the risks of adverse effects of the treatment. This information should allow patients to make more fully informed decisions about when they wish to start treatment.

Any doctors interested in collaborating in an MRC sponsored randomised study of early and deferred treatment in patients with single seizures or early epilepsy should contact me.

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The World Health Organisation

WHO's special programmes: undermining from above

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This is the sixth in a series examining the role of the World Health Organisation, its current problems, and its future prospects.

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Despite the World Health Organisation's spoken commitment to developing integrated primary health care, its most visible and successful activities are not integrated within countries; they are its disease specific intervention programmes, such as the Global Programme on AIDS and the programmes for the control of diarrhoeal and acute respiratory diseases. The 10 or so special programmes, all but one of which (the onchocerciasis control programme) are based in Geneva, have found increasing favour among donors, but critics say that they undermine WHO's attempts to integrate its activities at country level and discourage countries from developing their own capacity.

WHO's special programmes were set up in response to the perceived need among donors for something more comprehensive than WHO's regional and country based activities could offer. The idea is that they boost the organisation's routine activities, using international and regional expertise and a project based approach to attack specific diseases or health issues. The special programmes receive no funds from WHO's regular budget. They are funded from so called extrabudgetary contributions. Because of this they are not under the control of the director general, the executive board, or the World Health Assembly. Each special programme has its own director and a management executive committee made up of donors' representatives.

From the donors' point of view the special programmes have clear advantages over WHO's non-project based activities. They have well defined aims and strategies; they have outcome measures, even if most relate to process rather than health indicators; they are more financially accountable than the rest of WHO; and they are not under the direct control of the secretariat. This last point has become increasingly important in the past five years, according to diplomats in Geneva. As donors in Europe, Scandinavia, and America have become increasingly discontented with the organisation's lack of leadership and accountability they have concentrated their funding of WHO more and more in extrabudgetary donations. Extrabudgetary payments to special programmes now make up over half of the organisation's total income, compared with a quarter in 1972.

The shift to extrabudgetary funding restores to donor countries much of the influence they lost during the 1970s, when the influx into WHO of countries from the developing world more than doubled its membership. All countries have equal voting rights at the