The Management of Epilepsy in the 1990s
Acquisitions, Uncertainties and Priorities for Future Research
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Summary
The pharmacological treatment of epilepsy has made considerable progress during the last decade, due to improved knowledge of the clinical pharmacology of individual drugs, acquisition of new information on the factors affecting response and need for drug treatment, and development of promising new agents. Once a clinical diagnosis of epilepsy has been made (which generally requires the occurrence of more than one seizure), treatment should be started with a single drug selected on the basis of seizure type and tolerability profile. Although there are important regional differences in prescribing patterns and individual circumstances may dictate alternative choices, carbamazepine is generally regarded as the preferred treatment for partial seizures (with or without secondary generalisation) while valproic acid (sodium valproate) is usually the first choice in most forms of generalised epilepsies.

To achieve therapeutic success, the daily dosage must be tailored to meet individual needs, and there is suggestive evidence that in some patients the dosage prescribed initially may be unnecessarily large. Plasma antiepileptic drug concentrations may aid in the individualisation of dosage, but should not be regarded as a substitute for careful monitoring of clinical response.
Although overall about 70% of patients can be completely controlled, response rate is influenced by a number of factors, the most important of which are seizure type and syndromic form. The importance of a correct syndromic classification for rational drug selection has been poorly assessed and represents a major area for future research. Patients who do not respond to the highest tolerated dose of the initially prescribed drug may be switched to monotherapy with an alternative agent or may be given add-on treatment with a second drug. Appropriate prospective trials are required to assess the merits of either strategy. If add-on therapy is selected and the patient becomes seizure free, it may be possible to discontinue the drug prescribed initially and reinstitute monotherapy. Only a minority of patients are likely to require multiple drug therapy, and it remains to be established whether specific drug combinations are more effective than others.

Until further information becomes available, the new agents should be reserved for patients failing to respond to the conventional treatments of first choice. Patients whose seizures cannot be controlled by available drugs should be reassessed, and polytherapy should be maintained only when there is clear evidence that benefits outweigh possible adverse effects. In many patients who have been seizure free for at least 2 years it may be possible to gradually discontinue all medications. The decision to withdraw treatment is determined largely by the risk of seizure relapse which, in turn, is primarily dependent on the syndromic form.

Although other forms of treatment such as neurosurgery or biofeedback techniques may be of value to individual patients, antiepileptic drugs remain the mainstay for the management of epilepsy in the 1990s. However, the approach to pharmacological treatment of epileptic disorders has changed substantially in the past 30 years for several reasons: (i) the clinical pharmacology of antiepileptic drugs has been extensively investigated, with improved knowledge of the efficacy and tolerability of available products; (ii) the contribution of plasma drug concentrations has proved invaluable for a more correct monitoring of the risk/benefit ratio in individual patients; (iii) results of observational studies and clinical trials allow more rational therapeutic decisions for patients with a first unprovoked seizure, early epilepsy and prolonged remission of seizures; and (iv) new agents have been introduced which, although not shown to be superior to the old, time-honoured products, offer alternative options for difficult-to-treat patients.

Despite these advances, the modern treatment of epilepsy still leaves patients and physicians with uncertainties and controversies which provide the basis for further research in the field.

1. When to Start Treatment?

The decision to treat epilepsy is dependent on evidence of a positive impact of antiepileptic drugs on the risk of seizure relapse and/or prognosis of the disease. Although there has never been serious argument about the need for pharmacological treatment, until recently there has been little information on which to base a rational decision about the best timing at which treatment should be started.

The results of recent observational studies and clinical trials suggest that in most cases treatment should probably start after the first recurrence of seizures. While the pooled estimate of the risk of relapse after a first unprovoked tonic-clonic seizure is 42% at 2 years, after a second seizure the risk increases to between 79 and 96%. These data are in keeping with the standard definition of epilepsy, which implies the occurrence of relapsing unprovoked seizures, and support the concept that in a substantial proportion of individuals the first seizure tends to remain an isolated episode. The risk of seizure relapse varies among patients.