Seizures are the symptoms of a dysfunctional brain. They manifest in myriad different epilepsy syndromes with an equally wide variety of pathophysiologies. In the developed world, the majority of patients with newly diagnosed epilepsy will be started on a prophylactic treatment with an antiepileptic drug (AED). AEDs can only suppress seizure activity after epilepsy has developed, but none has been proven to influence the dynamic processes leading to epileptogenesis. When epilepsy remains uncontrolled, it is termed refractory or pharmacoresistant. It has long been recognised that seizures will be or will become refractory to pharmacotherapy in more than 30% of patients, and that localised related epilepsies are less likely to be controlled than the idiopathic generalised syndromes. Some of these patients will be offered epilepsy surgery or a vagal nerve stimulator. Many epilepsy sufferers will remain seizure-free on the first or second drug chosen. However, combinations of AEDs are usually prescribed in those unresponsive to monotherapy. The major dilemma inherent in this sequential approach of drug prescription lies in the imprecise understanding and definition of pharmacoresistance.

The ignorance of the neurobiological factors underlying the development of drug resistance in localisation-related epilepsy leads to an inability to individualise the prognosis. At present, it is only possible to guess at crude outcomes in patients with identified causative pathologies, such as cortical dysplasia (CD) and mesial temporal sclerosis (MTS), which often — but not always — carry a poor prognosis. Indeed, evidence of MTS has been found in patients without seizures.

Pharmacoresistance may be regarded as the flip-side of epileptogenesis. Recent research has focused on the role of multidrug transport systems, most notably P-glycoprotein (P-gp), in the pathogenesis of refractory epilepsy. P-gp is an efflux transporter, encoded by the multidrug resistance-1 (MDR1) gene, which contributes to the integrity of the blood–brain barrier and actively extrudes a wide range of pharmacological agents, including AEDs, from mammalian cells. Speculation suggests that overexpression of P-gp and other drug transport proteins in the region of epileptic foci can prevent AEDs from reaching their site of action. Elevated expression of these transporters has been reported in the region of both CD and MTS tissue. Whether drug transporters represent the cause or effect of recurrent seizures is unclear and perhaps unimportant, given that experimental seizures can induce their expression and potentially reinforce inherent or acquired intractability.

**AEDs**

In the past decade, nine new AEDs have been licensed, substantially widening physicians’ choice, and the number of possible combinations is now almost limitless. However, a number of issues remains to be addressed:

- the number of trials of single AEDs that should be employed before the patient is treated with duo-therapy;
- the number of AEDs, either singly or in combination (and in how many combinations), that need to fail before the seizure disorder can be recognised as refractory and surgery considered;
- the stage at which epilepsy becomes pharmacoresistant to AED treatment and what determines success or failure with AED therapy; and
- whether there are clinical features that will allow prediction of subsequent ‘refractoriness’.

The responses and solutions to these issues depend on an understanding of the natural history of treated epilepsy.

**Natural History of Treated Epilepsy**

Epilepsy patients can be divided into two classes: easy and difficult-to-control ones. A long-term outcome study supports the hypothesis that patients with newly diagnosed epilepsy comprise two distinct populations. Approximately 60% have a good prognosis. They will become seizure-free on a modest or moderate dose of the first- or second-choice AED as monotherapy without developing intolerable side effects. Some of these will remain in remission after withdrawal of...
AED therapy. The other 30–40% have difficult-to-control epilepsy. These patients often have an underlying structural cerebral abnormality. They are more likely to have had a high number of seizures before treatment was initiated, a feature recognised increasingly as the result rather than the cause of the pathophysiological changes that later manifest as refractory epilepsy. Pharmacoresistant epilepsy may, therefore, be present de novo as well as evolving over time, and can be identified early when treatment with the first well-tolerated AED fails. Between these two subsets, there is a grey zone of patients who will respond to combination therapy.

Combination Therapy

Combining AEDs requires an understanding of their pharmacology, particularly their mechanisms of action. Other issues that need to be considered in planning a treatment schedule for the individual patient include spectrum of efficacy, side effect profile and propensity for adverse interactions. Although the mechanisms of action of all AEDs are not fully understood, they fall into a number of general categories. Drugs such as phenytoin, carbamazepine and lamotrigine act primarily by limiting sustained repetitive firing via blockade of voltage-gated sodium channels. This property is shared by some of the newer AEDs, such as oxcarbazepine and zonisamide. Ethosuximide uniquely reduces low-threshold T-calcium currents. A number of AEDs, such as the barbiturates and the benzodiazepines vigabatrin and tiagabine enhance the inhibitory action of γ-aminobutyric acid. Effects on calcium and potassium channels and reduction of glutamate-mediated excitation also contribute to the antiepileptic properties of many drugs. Many of the newer AEDs, especially gabapentin, topiramate, felbamate, zonisamide and probably also lamotrigine and levetiracetam, have multiple pharmacological effects.

Theoretically, seizure freedom can be achieved by combining drugs with different, overlapping or similar mechanisms of action, with the aim of finding a complementary formula for the individual patient. In patients with multiple-seizure types or difficult-to-control epilepsy, AEDs with differing pharmacological properties should be chosen. Patients with a single-seizure type may, in addition, respond to a pairing that influences an individual ion channel or neurotransmitter system in different ways. Although robust data evaluating the effectiveness of AED combinations are scarce, some regimens, such as sodium valproate with ethosuximide for absence seizures, sodium valproate with lamotrigine for partial-onset and generalised seizures and lamotrigine with topiramate for a range of seizure types, have been suggested in clinical and laboratory studies to have additive or even synergistic effects. There is emerging evidence that a wide range of combinations of two or perhaps three AEDs can be effective in some patients with difficult-to-control epilepsy.

Epilepsy Management – Practical and Theoretical Considerations

The most suitable AED for each patient should be chosen to maximise the chance of remission without producing side effects, given that life-long treatment may be required in a patient with often mild epilepsy. Failure on the first AED due to lack of efficacy implies refractoriness, as only 11% of such patients subsequently become seizure-free. It is unclear whether substituting or adding another AED is a more effective strategy in this situation. For practical purposes, a patient may be regarded as having refractory epilepsy when no seizure control is obtained with consecutive trials of two AEDs. The challenge facing the clinician is to improve the outcome for patients not responding to monotherapy by combining more appropriately modern AEDs with complementary modes of action or offering them early resective surgery. If a structural abnormality, such as MTS, can be identified on brain imaging, surgery should be considered. For most patients in whom epilepsy cannot be ‘cured’ by surgery, combination therapy should be employed early in the management process.

Conclusions

If clinical, molecular or genetic markers can be identified that will refine prediction of outcome, compounds can start to be developed that do not just prevent seizures, but will also hinder or reverse the insidious processes underlying the genesis of refractory epilepsy. In addition, certain proteins are providing scope for pharmacological exploitation, and the recent identification of polymorphism-related P-gp expression may aid prediction of a patient’s innate drug resistance. This is, however, the tip of the iceberg.

Many genes influence the disposition of and response to AEDs. It is unlikely that a single polymorphism in the MDR1 gene alone will be predictive of outcome. By characterising polymorphisms in all genes that encode proteins that influence AED pharmacokinetics or pharmacodynamics, it may be possible to predict efficacy and acceptable tolerability with a specific drug in a designated patient with a defined epilepsy syndrome. This may in turn advance the understanding of epileptogenesis itself. Hopefully, the many decades of trial and error in choosing AED therapy will slowly give way to a more scientific rationale in the choice of antiseizure drugs for people with localisation-related epilepsy and antiepileptogenic agents for those at risk of developing it.
Keppra® (levetiracetam) is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy.

References: 1. Glauser TA, Gauer LJ, Chen L, et al. Multicenter, double-blind, placebo-controlled trial of adjunctive levetiracetam (Keppra®) therapy (up to 60 mg/kg/day) in pediatric patients with refractory partial epilepsy. Epilepsia. 2004;45(suppl):186. 2. Data on file, UCB Pharma, Inc.
NAME OF THE MEDICINAL PRODUCT: Keppra® (levetiracetam) film-coated tablets and oral solution.

OFFICIAL NAME AND FORM OF PREPARATION: Keppra® film-coated tablets contain 250 mg or 500 mg of levetiracetam. Each ml of oral solution contains 100 mg levetiracetam. Probenecid is the active metabolite of levetiracetam. Clinical pharmacokinetic and pharmacodynamic properties of Keppra® are based on probenecid concentrations.

Therapeutic indications: Keppra® is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in adults and children from 4 years of age with epilepsy. Probenecid is indicated for the management of clinical pharmacokinetic and pharmacodynamic properties of Keppra®.

Usual dose: The initial therapeutic dose is 500 mg twice daily escalating by 500 mg twice daily and titrating as tolerated.

Dosage recommendations for children and adolescents:

- Children aged 4 to 11 years: The initial therapeutic dose is 500 mg twice daily escalating by 500 mg twice daily and titrating as tolerated.

- Adolescents aged 12 to 17 years: The initial therapeutic dose is 500 mg twice daily escalating by 500 mg twice daily and titrating as tolerated.

Dosage recommendations for patients with hepatic impairment:

- Patients with treatments with the dose may be required to be adjusted as follows:

  - Patients with mild hepatic impairment: No dose adjustment is required.
  - Patients with moderate hepatic impairment (Child-Pugh class B): A 50% reduction of the daily maintenance dose is recommended when the estimated creatinine clearance is <50 ml/min.
  - Patients with severe hepatic impairment (Child-Pugh class C): A 75% reduction of the daily maintenance dose is recommended when the estimated creatinine clearance is <30 ml/min.

Dosage recommendations for patients with renal impairment:

- Patients with moderate renal impairment (estimated creatinine clearance of 30 to 60 ml/min): The dose may be reduced by 50%.
- Patients with severe renal impairment (estimated creatinine clearance of <30 ml/min): The dose should be reduced by 100%.
- Patients with end-stage renal disease: The dose should be reduced by 100%.

Adjustment of the dose is recommended in elderly patients with compromised renal function (see leaflet are provided with Keppra). The daily dose is administered in two equally divided doses. Adults (>65 years) and adolescents (12 to 17 years) of 50 kg or more:

- Patients with renal impairment: The dose should be increased by 25% in patients with severe renal impairment (creatinine clearance <30 ml/min).
- Patients with end-stage renal disease: The dose should be reduced by 100%.

Dosing adjustment for adult patients with impaired renal function:

- Normal: No adjustment is required.
- Moderate: 500 mg twice daily.
- Severe: 250 mg twice daily.
- End-stage renal disease: 0 mg twice daily.

A 750 mg loading dose is recommended on the first day of treatment with Keppra®.

Dosage recommendations for children and adolescents:

- Infants and children less than 4 years: There are insufficient data to recommend the use of levetiracetam in this population.
- Children aged 4 to 11 years and adolescents 12 to 17 years: The dose should be increased by 50% in patients with severe renal impairment (creatinine clearance <30 ml/min).
- Adolescents aged 12 to 17 years: The dose should be increased by 50% in patients with severe renal impairment (creatinine clearance <30 ml/min).

Dosage recommendations for patients with hepatic impairment:

- Patients with mild hepatic impairment: No dose adjustment is required.
- Patients with moderate hepatic impairment: A 50% reduction of the daily maintenance dose is recommended when the estimated creatinine clearance is <50 ml/min.
- Patients with severe hepatic impairment: A 75% reduction of the daily maintenance dose is recommended when the estimated creatinine clearance is <30 ml/min.

Dosage recommendations for patients with renal impairment:

- Patients with moderate renal impairment: The dose may be reduced by 50%.
- Patients with severe renal impairment: The dose should be reduced by 100%.
- Patients with end-stage renal disease: The dose should be reduced by 100%.

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