The use of new antiepileptic drugs

David Chadwick DM, FRCP, Professor of Neurology, Department of Neurological Science, Liverpool University

J R Coll Physicians Lond 1999; 33: 328–332

Epilepsy, the commonest neurological disorders and the one with the longest established therapeutic potential, is heterogeneous in nature and should therefore benefit from the widest possible range of drugs with many different mechanisms of action.

The field of antiepileptic drug (AED) therapy has been unusual in being dominated by old drugs such as phenobarbitone (introduced in 1912), and phenytoin (introduced in 1938). Until recently, treatments such as carbamazepine and valproate, introduced into clinical practice in the early 1970s, were regarded as new drugs. They were developed from empirical screening programmes without an understanding of their mechanisms of action. It is now recognised that phenytoin and carbamazepine have effects on voltage-sensitive sodium channels to block repetitive firing of neurons, phenobarbitone allosterically enhances the affinity of γ-aminobutyric acid (GABA) for its inhibitory neurotransmitter, while valproate probably has multiple mechanisms of action including effects at sodium and calcium channels.

A number of new AEDs, some with novel mechanisms of action, have become available worldwide in the last decade. After an initial inevitable burst of enthusiasm, we are now reaching a stage at which a more realistic assessment of their effectiveness can be made. Purchasers of health care, in particular, increasingly demand information to show that new, and inevitably more expensive, drugs have benefits to justify their cost. As epilepsy is the most common neurological disorder, indiscriminate switching from old to new AEDs would have considerable economic implications. This is reflected by a survey in the UK in 1992 which showed that the new drugs represent only 7% of prescriptions to people with epilepsy but 39% of the total drug costs, which in turn account for one-third of direct medical costs.

To justify their extra expense, new AEDs need to demonstrate greater efficacy against particular seizure types or epilepsy syndromes, better tolerability and/or greater safety than existing therapies. More intangible aspects of their value may need to be taken into account in justifying their expense, such as ease of use and lack of important interactions with other drugs.

Efficacy

In the modern era, new AEDs receive regulatory approval as a result of placebo-controlled, add-on, double-blind studies, almost always in populations of patients with refractory partial epilepsies. These studies are open to considerable criticism, but in essence show that an individual drug, when used in combination with a number of other antiepileptics, is better than nothing (placebo), is reasonably well tolerated and apparently safe. These studies do not allow consideration of comparative efficacy and tolerability, nor do they define the range of effectiveness of a drug against different seizure types and syndromes.

Over 4,000 patients have been included in studies of new AEDs in placebo-controlled, add-on designs in refractory partial epilepsy. In an age when meta-analysis is becoming fashionable, some estimates of varying treatment effects of new AEDs can be made from these studies. For the purpose of this calculation, efficacy may be defined as the proportion of patients in parallel-group studies showing a 50% reduction from baseline in seizure frequency. This may be compared to the same rate in placebo-treated patients to give an odds ratio (OR). There is a trend towards differences in efficacy and tolerability, with drugs such as topiramate and vigabatrin (OR 3.5–4.0) appearing more effective but less well tolerated than drugs such as gabapentin and lamotrigine (OR 2.0–2.5). Any differences may, however, simply be due to the former drugs having been tested close to — and even above — their maximum tolerated dosage, while the latter have been studied in clinical trials much closer to minimum effective doses. Unfortunately, standard AEDs such as carbamazepine have rarely been studied in placebo-controlled, add-on studies in similar populations of patients. Valproate is the exception, and estimates of its efficacy may be broadly similar to those of newer drugs.

More clinically informative studies have become available since new drugs have received licences. Comparative studies of monotherapy against carbamazepine have been published for lamotrigine, vigabatrin, and gabapentin in drug-naïve patients presenting with partial epilepsy for the first time.
time. The results show broadly that none of the new drugs can claim greater efficacy than carbamazepine, and indeed vigabatrin appears significantly less efficacious. All three drugs are, however, better tolerated than carbamazepine, with fewer withdrawals because of adverse events. Equivalence of efficacy with better tolerability may potentially be sufficient to identify some of the newer drugs as genuine first-line drugs. This will, however, depend on tight and rigorous definitions of equivalence of efficacy, and a better understanding of the psychosocial and economic costs of drug failure due to intolerability. Lamotrigine currently has the best case for being considered a first-line drug, given better retention-time than carbamazepine in a population of newly diagnosed patients. This outcome reflects both efficacy and tolerability, and is therefore of considerable clinical relevance. The difference in favour of lamotrigine is of a similar order as that of carbamazepine over phenobarbitone.

Some AEDs are active in more than just the partial epilepsies. For example, vigabatrin may be highly effective in the treatment of infantile spasms, a malignant childhood epilepsy previously treated with steroids, often with severe adverse effects. Similarly, randomised clinical trials (RCTs) of felbamate, lamotrigine and topiramate support effectiveness in Lennox-Gastaut syndrome, an often refractory generalised childhood epilepsy. We may increasingly see newer AEDs moving to occupy niches in particular epilepsy syndromes, especially those for which there are no well-designed RCTs with standard agents. The known spectrum of activity of old and new AEDs is summarised in Fig 1.

**Safety**

Safety issues are rarely explored within the context of RCTs, but risks of rare, although potentially serious, idiosyncratic adverse effects, chronic toxicity, and teratogenicity may be identified during the course of post-marketing surveillance. Recent experience confirms the need for continued vigilance in this area.

Felbamate (not registered in the UK) has been associated with aplastic anaemia in between 1 in 3,000 and 1 and 5,000 patient exposures. The detection of such a risk clearly influences the value and use of a new drug.

Lamotrigine is associated with acute idiosyncratic skin reactions, though possibly less frequently than carbamazepine. These reactions are sometimes severe and include Stevens-Johnson and toxic epidermal necrolysis syndromes (risk of 1 in 1,000 exposures in adults). Co-medication with valproate undoubtedly increases the risk of all reactions. The elevation of lamotrigine levels by a pharmacokinetic interaction is apparently responsible. Modifying the titration to very slow dosage introduction appears to reduce but not abolish the risk.

Vigabatrin has been associated with occasional psychotic reactions and depression, and should probably be avoided in patients with a previous psychiatric history. More recently, evidence has been produced that prolonged high-dose treatment with
vigabatrin may cause severe and symptomatic irreversible visual field constriction\(^2\). Quantitative visual field assessment can reveal asymptomatic, usually nasal, visual field constriction associated with electoretinographic changes, in keeping with retinal cone system dysfunction\(^2\), in larger numbers of patients treated with vigabatrin. Further follow-up of 32 patients continuing monotherapy with vigabatrin and 19 patients continuing with carbamazepine from the RCT reported by Kalviainen\(^23\) showed that 41% of the former had visual field constriction compared to none treated with carbamazepine, indicating a causal relationship between long-term vigabatrin exposure and visual field loss.

Standard AEDs are all associated with an increased risk of major fetal abnormalities and anomalies. In the long term, some new drugs such as gabapentin, lamotrigine and vigabatrin may prove more satisfactory for women in the child-bearing years. Animal screening has not shown an increased incidence of problems associated with the standard drugs in this age group of women. How much reassurance should be taken from this remains to be seen, and it will clearly be many years before we can be confident about the relative risks to pregnancy from new and standard AEDs.

Ease of use

Standard AEDs have not always proved easy to use. Some, such as phenytoin and carbamazepine, have complex pharmacokinetics and considerable potential for drug interaction both with other AEDs and with other therapeutic substances, which contributes to the need for therapeutic drug monitoring\(^24\). They are enzyme inducers and therefore interact with oral contraceptives. In contrast, drugs such as gabapentin and vigabatrin, which possess simple pharmacokinetics, may avoid the necessity for AED monitoring, and particularly lend themselves to add-on treatment because of their lack of drug interaction. Some new AEDs (gabapentin, tiagabine) have relatively short pharmacokinetic half-lives, which may render the ideal of once or twice a day dosing inadvisable. Not all new AEDs are simple to use. The metabolism of lamotrigine, tiagabine and topiramate is accelerated by enzyme-inducing AEDs such as carbamazepine and phenytoin, necessitating higher dosage with these co-medications. More problematic is the potential for inhibition of lamotrigine metabolism by valproate; this has major clinical impact on the risk of acute idiosyncratic skin reactions (see above).

None of the new AEDs has potent enzyme-inducing or inhibiting properties of its own, although topiramate may have a mild effect in inducing oestrogen metabolism.

Other benefits of new antiepileptic drugs

We now have a much more comprehensive understanding of the mechanism of action of both new and standard AEDs\(^1\) (summarised in Table 1). This has led directly to the concept of rational polytherapy which suggests that combining drugs with different mechanisms of action may benefit patients. There is already some clinical evidence to support the concept. Thus, vigabatrin, a gabergic drug, which was tested in add-on trials largely in combination with sodium channel drugs (carbamazepine and phenytoin), seems to be one of the more effective add-on agents\(^4\), yet as monotherapy may be less effective than a sodium channel drug, carbamazepine\(^8,9\). In contrast, lamotrigine, another sodium channel drug, is less effective as add-on therapy when added to other sodium channel drugs, but may compare more favourably with carbamazepine as monotherapy.

At a more anecdotal level, the combination of valproate and lamotrigine may be particularly effective in the treatment of more refractory idiopathic generalised epilepsies, an effect unlikely to be explained purely by the pharmacokinetic interaction.

Thus, new drugs, with new mechanisms of action, may not simply have value in their own right as monotherapy, but may allow additional health gains because of their potential for rational use as add-on therapy.

Conclusions

Our current knowledge about new and standard AEDs is summarised in Table 2. New AEDs have significantly increased the choice of drug for patients with epilepsy. Currently, they are used mostly for patients with refractory partial epilepsy requiring polytherapy, where their better tolerability compared to longer-established drugs is beneficial. They may increasingly be used as monotherapy. There is no evidence of superior efficacy to existing first-line agents such as carbamazepine or valproate, but the newer AEDs may be

Table 1. Mode of action of antiepileptic drugs.

| Antiepileptic drug | Voltage sensitive sodium channels | Gabergic | Glutaminergic | Slow calcium currents | Other |
|--------------------|----------------------------------|----------|---------------|----------------------|-------|
| Phenobarbitone     | ?                                | +        |               |                      |       |
| Phenytoin          | +                                |          |               |                      |       |
| Ethosuximide       |                                  |          |               |                      |       |
| Carbamazepine      | +                                |          |               |                      |       |
| Lamotrigine        | +                                |          |               |                      |       |
| Valproate          | +                                |          |               |                      |       |
| Vigabatrin         |                                  |          |               |                      |       |
| Gabapentin         | +                                | +        |               |                      |       |
| Topiramate         | +                                | +        |               |                      |       |
| Tiagabine          |                                  |          |               |                      |       |
| Antiepileptic drug | Indications | Contraindications | Adult dosage | Optimal plasma levels | Dose-related | Idiosyncratic | Chronic |
|--------------------|-------------|-------------------|--------------|-----------------------|--------------|--------------|---------|
| Carbamazepine      | Drug of choice: Partial epilepsy | Idiopathic generalised epilepsy | 600–1,600 mg/day | 4–10 μg/ml. Gradual introduction because of autoinduction | Dizziness, diplopia, unsteadiness | Rash & acute hypersensitivity reactions. Aplastic anaemia (1,200,000) | Few well documented (hyponatraemia, nephropenia) |
| Clobazam           | Second-choice drug: Probable broad-spectrum AED. Useful for treating clusters of seizures | | 20–60 mg/day. Therapeutic & adverse effects may show tolerance | | Drowsiness & sedation, but less than other benzodiazepines | |
| Ethosuximide       | Second-choice drug: Absence persisting into adult life | Partial epilepsy & generalised tonic-clonic seizures | 0.5–2.0 g/day | 40–100 μg/ml | Nausea, drowsiness, dizziness | Rash & acute hypersensitivity reactions. SLE-like syndromes | |
| Felbamate          | Occasional use: Lennox-Gastaut syndrome | | 1,200–4,800 mg/day | | | |
| Gabapentin         | Second-choice drug: Partial epilepsies | | 900 mg–4.8 g/day | | Drowsiness, sedation | None known | Possible weight gain |
| Lamotrigine        | First-choice drug: Broad-spectrum for partial epilepsy B possibly generalised syndromes | | 100–800 mg/day | | Diplopia, dizziness, sedation | Rash & acute hypersensitivity (particularly with valproate co-medication) | |
| Lorazepam          | First-choice drug: Status epilepticus | | 0.1 mg/kg | | | |
| Oxcarbazepine      | Drug of choice: Partial epilepsy. Broadly comparable with CBZ | Idiopathic generalised epilepsy | 600–3,000 mg/day | 50–150 μmol/l | Dizziness, diplopia & unsteadiness, but less frequent than CBZ | Rash, less frequent than CBZ, 25% of patients sensitive to CBZ will be sensitive to OXP | Hypoatraemia |
| Phenobarbitaline   | Occasional use in partial B generalised epilepsies (excepting absence) & status | | 60–200 mg/day | 15–35 μg/ml. Limits often modified by tolerance | Drowsiness, sedation, unsteadiness. Adverse effects on cognition & behaviour | Rash | Tolerance, habituation. Dupuytrens contracture, connective tissue disorders |
| Phenytoin          | Second-choice drug: Partial epilepsy & generalised tonic-clonic seizures | | 200–600 mg/day | 10–20 μg/ml. Monitoring indicated when seizure control is poor or side effects | Drowsiness, ataxia, dysarthria. Rarely, abnormal movements | Rash & acute hypersensitivity reactions | Gum hyperplasia, coarsening of facial features, hirsutism, acne. SLE-like syndromes |
| Primidone          | Rarely used: Probable efficacy as PB | | 500–1,500 mg/day | As PB, to which it is metabolised | Drowsiness, sedation & unsteadiness. Adverse effects on cognition & behaviour | Rash | Tolerance, habituation. Dupuytrens contracture, connective tissue disorders |
| Tiaogabine         | Second-choice drug: Partial epilepsy | Idiopathic generalised epilepsy | 15–60 mg/day | | Dizziness, depression, tremor. Possible exacerbation of partial seizures at higher doses | | |
| Topiramate         | Second-choice drug: Broad-spectrum AED | | 100–800 mg/day | | Sedation, cognitive difficulty | | Renal calculi |
| Valproate (sodium) | First-choice drug: Broad-spectrum AED. May be less effective in partial epilepsy than CBZ | | 1–3 g/day | Of no value | Tremor, irritability, occasional confusion | Gastric intolerance, hepatotoxicity (are in adults), pancreatitis | Weight gain, atopia, insulin intolerance, polycystic ovarian syndrome |
| Vigabatrin         | Second-choice drug: Partial epilepsies. May be useful in adult survivors of West syndrome | Idiopathic generalised epilepsy | 1.5–6.0 g/day | Of no value | Depression | Psychosis | Weight gain, visual field constriction |

Table 2. Efficacy and toxicity of antiepileptic drugs.
better tolerated – a key consideration in patients presenting with seizures for the first time. Further comparative controlled trials with clinically important long-term outcomes are needed before any of the new drugs can legitimately replace carbamazepine or valproate. The exception is infantile spasm (West syndrome), for which vigabatrin may be seen as the best available treatment.

References

1 White HS. Mechanisms of antiepileptic drugs. In: Porter RJ, Chadwick D (eds). The epilepsies. New York: Butterworth-Heinemann 1997:1–30.
2 Jacoby A, Buck D, Baker G, McNamee T, et al. Uptake and costs of care for epilepsy: findings from a UK regional study. Epilepsia 1998;39:776–86.
3 Mignot G. Drug trials in epilepsy. Br Med J 1996;313:1158.
4 Marson AG, Kadir ZA, Hutton JL, Chadwick DW. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. Epilepsia 1997;38:859–80.
5 Efferink JA, Van Zwieten-Boot BJ. New antiepileptic drugs. Analysis based on number needed to treat shows differences between drugs studied. Br Med J 1997;314:603.
6 Brodie MJ, Richards A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Lancet 1995;345:476–9.
7 Reunanen M, Dam M, Yuen AW. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. Epilepsy Res 1996;23:149–55.
8 Chadwick D, Roi L, Kennedy KM. Vigabatrin (Sabril) as a first-line monotherapy in newly diagnosed epilepsy: a double-blind comparison with carbamazepine. Epilepsia 1996;37:6.
9 Kalviainen R, Alikia M, Saukkonen AM, Mervaala E, Riekkinen PJ Sr. Vigabatrin vs carbamazepine monotherapy in patients with newly diagnosed epilepsy. A randomized controlled study. Arch Neurol 1995;52:989–96.
10 Chadwick DW, Anhut H, Greiner MJ, Alexander MS, et al. A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. Neurology 1998;51:1282–8.
11 Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. Br Med J 1996;313:36–9.
12 Mattson RH, Cramer JA, Collins JF, Smith DB, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalised tonic-clonic seizures. N Engl J Med 1985;313:145–51.
13 Chiron C, Dulac O, Gram L. Vigabatrin withdrawal randomized study in children. Epilepsy Res 1996;25:209–15.
14 Vigevano F, Cillo MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized prospective study. Epilepsia 1997;38:1270–4.
15 Appleton RE, et al. The Infantile Spasm Study Group. Thornton L. Double blind comparison of vigabatrin versus placebo in newly diagnosed and previously untreated infantile spasms. Epilepsia 1996;37:125.
16 Feilbarmate Study Group. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). N Engl J Med 1993;328:29–33.
17 Motte J, Trevathan E, Arvidsson JFV, Barrera MN, et al. Lamotrigine for generalised seizures associated with the Lennox-Gastaut syndrome. The Lamictal Lennox-Gastaut Study Group. N Engl J Med 1996;337:1807–12.
18 Glauser TA. Preliminary observations on topiramate in paediatric epilepsies. Epilepsia 1997;38(Suppl 1):S37–41.
19 Stables JP, Bialer M, Johannessen SI, Kupperberg HJ, et al. Progress report on new antiepileptic drugs. A summary of the Second Eilat Conference. Epilepsy Res 1995;22:235–46.
20 Richens A. Vigabatrin and lamotrigine. In: Porter RJ, Chadwick D (eds). The epilepsies 2. New York: Butterworth-Heinemann 1997:201–22.
21 Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. Br Med J 1997;314:180–1.
22 Krauss GL, Johnson MA, Miller NR. Vigabatrin associated retinal cone system dysfunction: electroretinogram and ophthalmologic findings. Neurology 1998;50:614–8.
23 Kalviainen R, Nousiainen I, Mantyjarvi M, Riekkinen PJ. Initial vigabatrin monotherapy is associated with increased risk of visual field constriction. Epilepsia 1998;39(Suppl 6):72.
24 Richens A, Perucca E. Clinical pharmacology and medical treatment. In: Laidlaw J, Richens A, Chadwick D (eds). A textbook of epilepsy. Edinburgh: Churchill Livingstone, 1993:495–560.

Address for correspondence: Professor David Chadwick, Department of Neurological Science, Liverpool University, The Walton Centre for Neurology and Neurosurgery, Lower Lane, Liverpool L9 7LJ. E-mail: bessan-p@wcmn.co.uk