Tidsskriftet
DEN NORSKE LEGEFORENING

Are the new anti-epileptic drugs any better than their predecessors?

KRONIKK

KARL OTTO NAKKEN

E-mail: karln@ous-hf.no
Karl Otto Nakken MD PhD is a neurologist and retired senior consultant. For many years he was in charge of medical treatment at the National Centre for Epilepsy at Sandvika.
The author has completed the ICMJE form and declares the following conflict of interest: He has received lecture fees from Eisai.

EYLERT BRODTKORB

Professor Eylert Brodtkorb MD PhD is a neurologist at St Olav's Hospital, Trondheim University Hospital, with a long-standing interest in epileptic disorders.
The author has completed the ICMJE form and declares the following conflict of interest: He has received lecture fees from Eisai and UCB.

Since 1993, fifteen new anti-epileptic drugs have entered the market. But while the potential for personalised treatment has never been greater, the proportion of patients achieving seizure freedom is no higher than it was before.

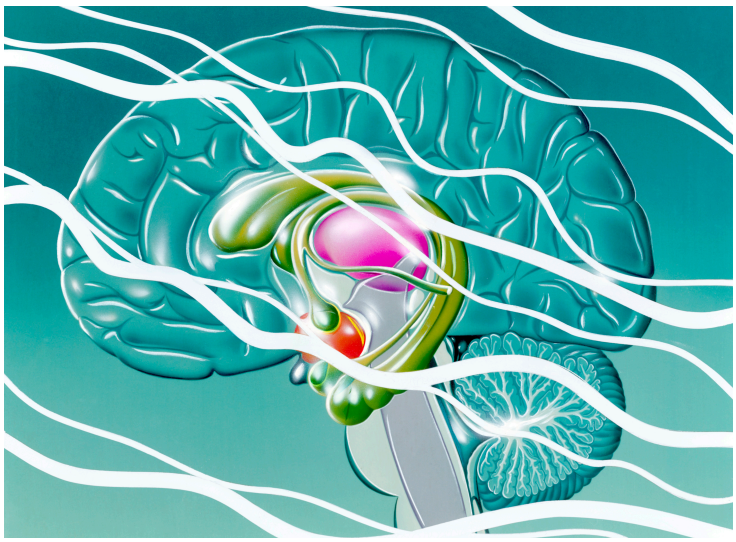

Illustration: Science Photo Library / NTB

Prior to 1993, the treatment of epilepsy was largely dominated by four drugs: phenobarbital, phenytoin, carbamazepine and valproate. But these drugs had little or no effect on seizures in about one third of patients, and some of them also produced troublesome side effects. The introduction of the new anti-epileptic drugs was therefore met with high hopes.

New mechanisms of action

While the older drugs exert their anti-seizure effects mainly by blocking neuronal sodium channels (phenytoin and carbamazepine) or by increasing GABAergic inhibition (phenobarbital and valproate), some of the new drugs have different mechanisms of action.

Vigabatrin increases GABAergic inhibition in the synapse by inhibiting the breakdown of GABA. In the presynaptic boutons of neurons, levetiracetam and brivaracetam bind to the synaptic vesicle protein SV2A, altering neurotransmitter release. Lacosamide enhances the slow inactivation of sodium channels, whereas perampanel blocks a glutamate receptor, AMPA. Gabapentin, pregabalin and to some extent zonisamide act as calcium channel blockers. Some of the new drugs represent only minor structural modifications of older ones (oxcarbazepine, eslicarbazepine, pregabalin, brivaracetam) (1).

In common with their predecessors, the new drugs provide only symptomatic treatment in the form of seizure prophylaxis; they do not affect the epilepsy per se.

New drugs no more effective than the old ones

Although each drug must be considered on its own merits, the overall evidence indicates that using the new drugs as monotherapy has *not* increased the proportion of seizure-free patients (2). In 2013, the International League Against Epilepsy reviewed 11 meta-analyses and 64 randomised clinical trials comparing the efficacy of the old versus new drugs. The conclusion was clear: the new drugs have *not* reduced the proportion of pharmacoresistant patients (3). Similar studies conducted after 2013 have not shaken that conclusion (4, 5).

A Scottish study showed that in 2000, around 64 % of 470 patients with new-onset epilepsy achieved seizure freedom for at least one year, mainly with the older drugs (6). But that percentage was no higher among 1 795 patients in 2014, after the new drugs had been introduced (7).

In our experience, several of the new drugs have little effect on seizure frequency, but they reduce seizure severity

In most studies, the new drugs have been compared with carbamazepine in the form of extended-release tablets. Levetiracetam, zonisamide, lacosamide and eslicarbazepine have been found to be as efficacious as phenytoin and carbamazepine (level 1 evidence) in adults with focal epilepsy. In elderly patients with new-onset focal epilepsy, lamotrigine and levetiracetam were as efficacious as carbamazepine (8).

Meta-analyses of randomised clinical trials in children and adolescents with new-onset focal seizures have shown no difference in efficacy between phenobarbital, phenytoin, carbamazepine and valproate, or between lamotrigine and oxcarbazepine. A slight trend was seen in favour of carbamazepine and lamotrigine (9). In childhood absence epilepsy, ethosuximide and valproate were shown to be superior to lamotrigine (10).

Other positive effects

Although the goal of all epilepsy treatment is seizure freedom, the value of other beneficial effects should not be underestimated. In our experience, several of the new drugs have little effect on seizure *frequency*, but they reduce seizure *severity*. Some patients become free of major tonic-clonic seizures, for example, which virtually eliminates their risk of sudden unexpected death (11). Others find that their seizures become shorter with faster postictal recovery. Combination therapy, particularly with agents that have different mechanisms of action, can be beneficial in some cases (2). The availability of an increased selection of drugs with different pharmacodynamic profiles means that individual patient vulnerabilities can also be taken into account.

Affective disorders are not uncommon among the epilepsy population. Some patients with epilepsy may therefore benefit from the mood-stabilising effects of lamotrigine or the

anxiolytic effects of pregabalin.

More favourable pharmacokinetics

The old drugs have several drawbacks in terms of their pharmacokinetics. Phenytoin and carbamazepine exhibit non-linear kinetics: phenytoin shows saturation kinetics while carbamazepine shows dose-related autoinduction. The old drugs are metabolised by enzymes that may be subject to induction (phenytoin, carbamazepine and phenobarbital) or inhibition (valproate). This introduces the possibility of pharmacokinetic interactions between these drugs, or with other drugs (12).

Most of the new drugs have more favourable pharmacokinetic profiles with less potential for interactions. Many exhibit linear pharmacokinetics, resulting in a predictable relationship between dose and serum concentration. Some have argued that this makes the measurement of serum concentration unnecessary, but such measures have proved useful in many situations. For example, women who begin taking oral contraceptives or who become pregnant may experience a reduction of up to 50 % in their serum concentration of lamotrigine (13). Both old and new drugs are also subject to significant pharmacokinetic variation.

One disadvantage of several of the new agents is that they have a relatively short half-life. This means that at least two daily doses are required, which increases both the risk and the consequences of missed doses.

Better side-effect profile?

The old drugs are associated with a number of unfortunate long-term side effects. Phenobarbital, for example, can cause Dupuytren's contracture, while phenytoin can give rise to gingival hyperplasia, carbamazepine can cause osteoporosis, and valproate can have endocrine and teratogenic effects (14).

The new drugs are not without side effects either, but in our experience most of these drugs are reasonably well tolerated. Some of the new drugs *can* have neuropsychiatric side effects, however, especially levetiracetam, perampanel and topiramate, and to some extent also brivaracetam (15).

Although the results vary somewhat, several trials show higher retention rates with the new drugs than with carbamazepine. This is primarily due to better tolerability (8). In the Scottish study that followed up patients for almost 30 years, however, the proportion of early discontinuations due to side effects remained unchanged despite increasing use of newer drugs (16).

New drugs have reduced the incidence of fetal damage

A meta-analysis found that the use of valproate in pregnancy led to congenital malformations in 10.9 % of cases, with the risk increasing with increasing dose (17). In addition, children that have been exposed to valproate have been shown to score more poorly on IQ tests than children exposed to other seizure-suppressing drugs during gestation (18), and to be at increased risk of developing autism (19).

Once this had been established, the health authorities issued a warning about the use of valproate in pregnancy (20). Among women who wished to conceive, the use of valproate was largely replaced by use of lamotrigine and levetiracetam, leading to a 27 % reduction in the prevalence of malformations from 2000–05 to 2010–13 (21). Experience with use of the newest drugs during pregnancy is currently limited.

Special indications

Some of the new drugs are niche drugs. Dravet syndrome and Lennox-Gastaut syndrome are

serious epileptic encephalopathies for which the old medications were largely ineffective. Three drugs have proved particularly efficacious for these syndromes: stiripentol, rufinamide and cannabidiol (22). Cannabidiol is not currently marketed in Norway, and long-term data are limited.

What's the current outlook?

We have no option but to conclude that the new anti-epileptic drugs have not lived up to expectations in terms of increasing the proportion of seizure-free patients. At the individual level, however, many patients have had good experiences with the new drugs. There are also increased options for personalised treatment with the aim of achieving a more favourable balance between efficacy and adverse effects than was possible in the past. Unfortunately, seizure freedom is only achieved in about two-thirds of patients.

It may appear that no further progress can be made using drugs with traditional mechanisms of action, namely modulation of neuronal synaptic transmission. Attention has turned recently to other approaches, including targeting glial cells, neuroinflammation and genetic mechanisms (2, 23). Treatments that target the effects of single mutations are now being developed for a number of rare diseases associated with epilepsy (e.g. GLUT1 deficiency syndrome, pyridoxine-dependent epilepsy, tuberous sclerosis and certain channelopathies) (24). Perhaps we are on the cusp of a new era in epilepsy treatment involving a mechanistic approach based on close neuroscientific collaboration between clinicians and basic researchers.

REFERENCES:

1. Kobayashi K, Endoh F, Ohmori I et al. Action of antiepileptic drugs on neurons. Brain Dev 2020; 42: 2–5. [PubMed][CrossRef]

2. Perucca E, Brodie MJ, Kwan P et al. 30 years of second-generation antiseizure medications: impact and future perspectives. Lancet Neurol 2020; 19: 544–56. [PubMed][CrossRef]

3. Glauser T, Ben-Menachem E, Bourgeois B et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2013; 54: 551–63. [PubMed][CrossRef]

4. Baulac M, Rosenow F, Toledo M et al. Efficacy, safety, and tolerability of lacosamide monotherapy versus controlled-release carbamazepine in patients with newly diagnosed epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. Lancet Neurol 2017; 16: 43–54. [PubMed][CrossRef]

5. Trinka E, Ben-Menachem E, Kowacs PA et al. Efficacy and safety of eslicarbazepine acetate versus controlled-release carbamazepine monotherapy in newly diagnosed epilepsy: A phase III double-blind, randomized, parallel-group, multicenter study. Epilepsia 2018; 59: 479–91. [PubMed][CrossRef]

6. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000; 342: 314–9. [PubMed][CrossRef]

7. Chen Z, Brodie MJ, Liew D et al. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol 2018; 75: 279–86. [PubMed][CrossRef]

8. Werhahn KJ, Trinka E, Dobesberger J et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. Epilepsia 2015; 56: 450–9. [PubMed][CrossRef]

9. Rosati A, Ilvento L, Lucenteforte E et al. Comparative efficacy of antiepileptic drugs in children and adolescents: A network meta-analysis. Epilepsia 2018; 59: 297–314. [PubMed][CrossRef]

10. Glauser TA, Cnaan A, Shinnar S et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. Epilepsia 2013; 54: 141–55. [PubMed][CrossRef]

11. Sveinsson O, Andersson T, Mattsson P et al. Clinical risk factors in SUDEP: A nationwide population-

based case-control study. Neurology 2020; 94: e419–29. [PubMed][CrossRef]

12. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic Disord 2014; 16: 409–31. [PubMed][CrossRef]

13. Ding Y, Tan X, Zhang S et al. Pharmacokinetic changes and therapeutic drug monitoring of lamotrigine during pregnancy. Brain Behav 2019; 9: e01315. [PubMed][CrossRef]

14. Svendsen T, Alfstad KÅ, Lossius MI et al. Langtidsbivirkninger av antiepileptika. Tidsskr Nor Legeforen 2016; 136: 324–7. [PubMed][CrossRef]

15. Hansen CC, Ljung H, Brodtkorb E et al. Mechanisms underlying aggressive behavior induced by antiepileptic drugs: focus on topiramate, levetiracetam, and perampanel. Behav Neurol 2018; 2018: 2064027. [PubMed][CrossRef]

16. Alsfouk BAA, Brodie MJ, Walters M et al. Tolerability of antiseizure medications in individuals with newly diagnosed epilepsy. JAMA Neurol 2020; 77: 574–81. [PubMed][CrossRef]

17. Weston J, Bromley R, Jackson CF et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev 2016; 11: CD010224. [PubMed][CrossRef]

18. Baker GA, Bromley RL, Briggs M et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology 2015; 84: 382–90. [PubMed][CrossRef]

19. Christensen J, Grønborg TK, Sørensen MJ et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 2013; 309: 1696–703. [PubMed][CrossRef]

20. European Medicines Agency. Valproate and related substances. https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0 Accessed 11.9.2020.

21. Tomson T, Battino D, Bonizzoni E et al. Declining malformation rates with changed antiepileptic drug prescribing: An observational study. Neurology 2019; 93: e831–40. [PubMed][CrossRef]

22. Mudigoudar B, Weatherspoon S, Wheless JW. Emerging antiepileptic drugs for severe pediatric epilepsies. Semin Pediatr Neurol 2016; 23: 167–79. [PubMed][CrossRef]

23. Patel DC, Tewari BP, Chaunsali L et al. Neuron-glia interactions in the pathophysiology of epilepsy. Nat Rev Neurosci 2019; 20: 282–97. [PubMed][CrossRef]

24. Perucca P, Perucca E. Identifying mutations in epilepsy genes: Impact on treatment selection. Epilepsy Res 2019; 152: 18–30. [PubMed][CrossRef]

Published: 23 November 2020. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.20.0657
Received 26.8.2020, first revision submitted 30.8.2020, accepted 11.9.2020.