Comparative Monotherapy Trials and the Clinical Treatment of Epilepsy

Comparison of Levetiracetam and Controlled-Release Carbamazepine in Newly Diagnosed Epilepsy. Brodie MJ, Perucca E, Ryvlin P, Ben-Menachem E, Meencke HJ; Levetiracetam Monotherapy Study Group. *Neurology* 2007;68(6):402–408. OBJECTIVE: We report the results of a prospective study of the efficacy and tolerability of levetiracetam, a new antiepileptic drug with a unique mechanism of action, in comparison with controlled-release carbamazepine as first treatment in newly diagnosed epilepsy. METHODS: Adults with 2 partial or generalized tonic–clonic seizures in the previous year were randomly assigned to levetiracetam (500 mg twice daily, $n = 288$) or controlled-release carbamazepine (200 mg twice daily, $n = 291$) in a multicenter, double-blind, noninferiority, parallel-group trial. If a seizure occurred within 26 weeks of stabilization, dosage was increased incrementally to a maximum of levetiracetam 1,500 mg twice daily or carbamazepine 600 mg twice daily. Patients achieving the primary endpoint (6-month seizure freedom) continued on treatment for a further 6-month maintenance period. RESULTS: At per-protocol analysis, 73.0% (56.6%) of patients randomized to levetiracetam and 72.8% (58.5%) receiving controlled-release carbamazepine were seizure free at the last evaluated dose (adjusted absolute difference 0.2%, 95% CI – 7.8% to 8.2%) for 6 months (1 year). Of all patients achieving 6-month (1-year) remission, 80.1% (86.0%) in the levetiracetam group and 85.4% (89.3%) in the carbamazepine group did so at the lowest dose level. Withdrawal rates for adverse events were 14.4% with levetiracetam and 19.2% with carbamazepine. CONCLUSIONS: Levetiracetam and controlled-release carbamazepine produced equivalent seizure freedom rates in newly diagnosed epilepsy at optimal dosing in a setting mimicking clinical practice. This trial has confirmed in a randomized, double-blind setting previously uncontrolled observations that most people with epilepsy will respond to their first-ever antiepileptic drug at low dosage.

COMMENTARY

With the exception of oxcarbazepine and felbamate, all of the new antiepileptic drugs were approved initially as adjunctive therapy for partial epilepsy; approval was based on placebo-controlled, add-on trials involving patients with refractory epilepsy. In these trials, the main outcome measures were improvement in seizure frequency over baseline and the proportion of patients with 50% or greater reduction in seizure frequency. Superiority over placebo in add-on trials does not necessarily predict that an antiepileptic drug will be effective and well tolerated as an initial monotherapy. Confirmation for use of an antiepileptic drug as first-line treatment requires a sound monotherapy trial with newly diagnosed patients. In addition, the practicing physician would need to feel assured that the new antiepileptic drug is not less effective than established, standard therapy. Large, comparative antiepileptic drug trials are necessary to provide that assurance. The two large, cooperative VA comparative trials have played a major role in developing guidelines for the older antiepileptic drugs and propelled carbamazepine to the position of being the favored initial agent for the treatment of partial epilepsy (1,2). Consequently, carbamazepine has become the customary active control used for comparative, first-line, monotherapy trials of lamotrigine, oxcarbazepine, and gabapentin (3–6).

Levetiracetam is one of the most widely used add-on antiepileptic medications. Some of its advantages include rapid

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and almost complete absorption, initiation at an effective dose, absence of hepatic metabolism, absence of enzyme induction, absence of clinically significant interactions, and the availability of an intravenous formulation (7,8). Several published open-label reports of successful initial monotherapy administration of levetiracetam begged for a formal, blinded, and randomized trial to support this practice. The current study by Brodie et al. addresses this issue, is well powered, and also distinguishes itself from previous comparative trials by using a controlled-release preparation of carbamazepine as well as flexible dosing. Controlled-release carbamazepine is better tolerated owing to less fluctuation in plasma levels. Levetiracetam and controlled-release carbamazepine were equally effective with respect to seizure freedom at 6 months and 1 year of treatment. With both antiepileptic drugs, most patients became seizure free at the lowest dose level. Overall, more patients discontinued therapy because of adverse experiences in the carbamazepine group, but the difference did not reach significance, and the two drugs showed a similar proportion of patients who had at least one adverse experience. The levetiracetam-treated group more often reported depression and insomnia, while the carbamazepine group more often reported back pain, which is hard to explain. There also was greater weight gain with carbamazepine than levetiracetam.

The results of this trial earned levetiracetam approval as a first-line monotherapy in the treatment of partial epilepsy in the European Union, but not in the United States. Approval of antiepileptic drugs by the U. S. Food and Drug Administration (FDA) requires demonstration of superiority over another treatment or over placebo and may not be based on equivalent efficacy. In adjunctive trials, demonstration of superiority is straightforward, with placebo used as a comparator, and since baseline antiepileptic medications are continued, there are no ethical issues involving the use of placebo. In contrast, the use of placebo as monotherapy for epilepsy does raise ethical concerns, and superior efficacy has never been demonstrated for a new antiepileptic drug in comparison with the old antiepileptic drugs. As a result of these difficulties, few drugs have earned initial monotherapy indication in the United States. One concern raised by the FDA in relation to equivalence trials is that it is possible that in a specific population studied, equivalence could be due to equal lack of efficacy (9). However, the proportion of seizure-free patients should help evaluate this possibility. One epidemiologic study suggested that the risk of seizure recurrence at 1 year is 57%, after two unprovoked seizures, and 61%, following three unprovoked seizures (10). Most patients in this epidemiologic study received treatment, and the chance of remaining seizure-free for 1 year without treatment must be less than 40%. The 1-year seizure-free rate of 56.6% to 58.5% in the study by Brodie and colleagues is significantly better than expected ($p = 0.001$) and represents evidence that both antiepileptic drugs were effective.

The Therapeutics and Technology Assessment Subcommittee and the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society accepted large, blinded, and randomized comparative studies in its assessment of the new antiepileptic drugs (11). Its 2004 recommendation was that patients with recently diagnosed partial epilepsy who require treatment can be initiated on lamotrigine, gabapentin, oxcarbazepine, or topiramate (11). The current trial likely will add levetiracetam to that list. As a result of the growing list of antiepileptic drugs that can now be considered for first-line treatment, there is a need to develop guidelines. Such guidelines ideally should be determined by comparative trials that evaluate relative efficacy and tolerability of the new antiepileptic drugs. However, choice of first-line antiepileptic drugs also should take into consideration factors such as the acuteness of the epilepsy, the need for rapid titration, the need to avoid interactions, as well as associated comorbid conditions. In the future, an important criterion in the selection of the first antiepileptic drug for a patient may be its antiepileptogenic potential, which is the ability of a drug to arrest, delay, or reverse the development of epilepsy. Some antiepileptic drugs, such as valproate and levetiracetam, demonstrated an antiepileptogenic action in animal models of epilepsy, particularly suppressing the development of kindling. However, valproate failed to demonstrate an antiepileptogenic effect in patients with head trauma or brain tumors (12), and no drug has been demonstrated to have an antiepileptogenic effect in human epilepsy. In recent onset epilepsy, it is possible that epileptogenesis could still be active. An antiepileptogenic drug could potentially influence the course of the epilepsy, perhaps to the degree that seizures do not recur after antiepileptic drug withdrawal. If seizure-free patients in the trial of Brodie and colleagues continue to be followed after drug discontinuation, this trial may help provide data on whether levetiracetam has antiepileptogenic effects in recently diagnosed partial epilepsy. If treatment with levetiracetam is associated with less seizure recurrence on discontinuation, this finding could be evidence of an antiepileptogenic effect and potentially be a very important factor in choosing the first treatment for epilepsy.

by Bassel W. Abou-Khalil, MD

References

1. Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. *N Engl J Med* 1992;327:765–771.

2. Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, Williamson PD, Treiman DM, McNamara JO, McCutchen CB, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med* 1985;313:145–151.
3. Reinikainen KJ, Keranen T, Halonen T, Komulainen H, Riekkinen PJ. Comparison of oxcarbazepine and carbamazepine: a double-blind study. *Epilepsy Res* 1987;1:284–289.
4. Dam M, Ekberg R, Loyning Y, Waltimo O, Jakobsen K. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. *Epilepsy Res* 1989;3:70–76.
5. Rowan AJ, Ramsay RE, Collins JF, Pryor F, Boardman KD, Uthman BM, Spitz M, Frederick T, Towne A, Carter GS, Marks W, Felicetta J, Tomyanovich ML. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology* 2005;64:1868–1873.
6. Chadwick DW, Anhut H, Greiner MJ, Alexander J, Murray GH, Garofalo EA, Pierce MW. A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. International Gabapentin Monotherapy Study Group 945–77. *Neurology* 1998;51:1282–1288.
7. Baulac M, Brodie MJ, Elger CE, Krakow K, Stockis A, Meyvisch P, Falter U. Levetiracetam intravenous infusion as an alternative to oral dosing in patients with partial-onset seizures. *Epilepsia* 2007;48:589–592.
8. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther* 2000;85:77–85.
9. Leber PD. Hazards of inference: the active control investigation. *Epilepsia* 1989;30(suppl 1):S57–S63; discussion S64–S58.
10. Hauser WA, Rich SS, Lee JR, Annegers JF, Anderson VE. Risk of recurrent seizures after two unprovoked seizures. *N Engl J Med* 1998;338:429–434.
11. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Theodore WH, Bazil C, Stern J, Schachter SC, Bergen D, Hirtz D, Montouris GD, Nespeca M, Gidal B, Marks WJ Jr, Turk WR, Fischer JH, Bourgeois B, Wilner A, Faught RE Jr, Sachdeo RC, Beydoun A, Glauser TA. Efficacy and tolerability of the new antiepileptic drugs, I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2004;62:1252–1260.
12. Temkin NR, Jarell AD, Anderson GD. Antiepileptogenic agents: how close are we? *Drugs* 2001;61:1045–1055.