Open Comparative Long-term Study of Vigabatrin vs Carbamazepine in Newly Diagnosed Partial Seizures in Children

Nelia Zamponi, MD; Cesare Cardinali, MD

Objective: To compare vigabatrin with carbamazepine as monotherapy in newly diagnosed children with partial epilepsy in order to evaluate the efficacy and tolerability of both drugs.

Design: Open and randomized with a 2-year follow-up period.

Setting: The Infantile Neuropsychiatric Division of the Regional Pediatric Hospital, Ancona, Italy.

Patients: Seventy children with newly diagnosed partial epilepsy were treated with vigabatrin (38 patients) or carbamazepine (32 patients).

Intervention: Vigabatrin, 50 to 60 mg/kg per day, or carbamazepine, 15 to 20 mg/kg per day, split into twice-a-day doses.

Outcome Measures: The efficacy and tolerability of vigabatrin were compared with those of the standard treatment (carbamazepine) for this patient group.

Results: The efficacy of vigabatrin and carbamazepine was similar, with the suggestion of a better side effect profile with vigabatrin.

Conclusions: Vigabatrin monotherapy should be considered as a monotherapeutic treatment option in patients with newly diagnosed epilepsy. However, more studies are needed to evaluate other issues of concern, such as the cognitive and behavioral adverse effects of antiepileptic drugs, to determine the most suitable therapy.

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Among the various new antiepileptic drugs, vigabatrin is widely used for the treatment of drug-resistant epilepsy in both adults and children. The accumulating data on vigabatrin affirm the therapeutic value of the drug, with positive results (disappearance or reduction of seizures in >50% of patients) occurring in approximately 30% to 40% of patients. The varying values that have been reported may, to some degree, reflect the different methods of patient recruitment and the varying definitions of drug resistance that have been used in the studies. Furthermore, vigabatrin is well tolerated, with only rare reports of serious adverse effects.

Vigabatrin is still not being used as monotherapy in children, except in those with West syndrome, for whom vigabatrin is one of the most commonly prescribed drugs. Few reports exist regarding the efficacy and tolerability of vigabatrin monotherapy in patients with newly diagnosed partial epilepsy.

Results

Vigabatrin Group

Regarding clinical efficacy, 9 relapses (23.7%) occurred: 7 within the first 6 months of the study and the other 2 within 1 year. In patients with relapses, carbamazepine was substituted for vigabatrin (5 cases), or another drug was administered in addition to vigabatrin (4 cases). Complete control of seizures after this therapy modification was obtained in 1 case (in which the patient was receiving carbamazepine monotherapy). The epilepsy was cryptogenic in 3 cases and symptomatic in 6 cases. The EEG showed a significant reduction of paroxysmal abnormalities within the first 6 months of therapy in 5 cases.

The most frequent adverse effect was irritability/excitability, occurring in 6 cases (15.8%), but discontinuation of vigabatrin therapy was necessary in only 1 patient, who exhibited antisocial behavior. Weight increases of 10% to 20%...
PATIENTS AND METHODS

A total of 70 children with newly diagnosed partial epilepsy were admitted to the Infantile Neuropsychiatric Division of the Regional Pediatric Hospital, Ancona, Italy, and treated with vigabatrin or carbamazepine in an open, randomized comparative study.

All the patients underwent hematologic examinations, including baseline hormone assessment (thyroid hormones, growth hormone, and cortisol levels), electroencephalography (EEG), ophthalmoscopic evaluation, neurologic examination, and neuroradiologic tests. Regular physical and neurologic examinations, EEG, and hematologic tests were carried out throughout the 2-year follow-up (at 1, 3, 6, 12, 18, and 24 months). There was a titration period of 4 weeks for both the carbamazepine and the vigabatrin groups. The starting dose for carbamazepine was 5 mg/kg per day, and the dose was progressively increased at 3- to 4-day intervals. The starting dose for vigabatrin was 10 to 15 mg/kg per day, and the dose was progressively increased at 2- to 3-day intervals.

VIGABATRIN GROUP

In the vigabatrin group, 38 patients (21 boys and 17 girls; mean age, 7 years 4 months; range, 6 months to 10 years 3 months) were treated with vigabatrin, 50 to 60 mg/kg per day split into twice-a-day doses. In 35 cases, epilepsy had occurred less than 1 month earlier. One patient presented with seizures 1 year 6 months before hospitalization, and 2 patients had suffered neonatal seizures 3 years earlier. Twelve patients had partial idiopathic epilepsy; 10 patients had a cryptogenic form; and 10 patients had a symptomatic form. The number of seizures before the start of therapy was less than 10 in 30 cases, 10 to 50 in 5 cases, and more than 50 in 3 cases (1 with frontal seizures and 2 with complex partial seizures plus spasms). The types of seizure were complex partial (17 cases); partial, secondarily generalized (18 cases); unilateral (hemiconvulsion) (1 case); and partial plus spasms (2 cases).

In 30 cases, vigabatrin was administered as a first-choice drug, while in 8 cases it replaced another antiepileptic drug therapy that had been started less than 1 month before. In 6 cases, the previous therapy was carbamazepine, which had been discontinued because of the early appearance of rash (4 patients) or lack of efficacy (2 patients). One patient was given clobazam and another valproate sodium. Both patients had relapses during the first month of treatment.

The EEG demonstrated focal epileptiform activity in 24 cases, multifocal abnormalities in 5, and important bilateral diffusion in 2. In 7 cases, no alterations were identified. The results of neurologic evaluation were normal in 28 cases, and in 26 cases neuropsychiatric evaluation did not show any learning or behavioral problems.

CARBAMAZEPINE GROUP

In the carbamazepine group, 32 patients (17 boys and 15 girls; mean age, 9 years 5 months; range, 3 years to 13 years 2 months) were treated with carbamazepine, controlled-release tablets, 1520 mg/kg per day split into twice-a-day doses. The prescribed dose of carbamazepine did not exceed serum levels of 10 µg/mL (normal range, 5-10 µg/mL). In 27 patients, epilepsy had occurred less than 1 month before; 2 patients presented with seizures 2 years earlier; and 3 patients had presented with febrile convulsions. Nine patients had partial idiopathic epilepsy, 16 had a cryptogenic form, and 7 had symptomatic epilepsy. The number of seizures before therapy was less than 10 in 28 patients and 10 to 50 in 4 patients. The types of seizures were complex partial (13 cases); partial, secondarily generalized (14 cases); and partial elementary (3 cases).

The EEG revealed focal epileptiform activity in 15 cases and multifocal abnormalities in 12; the results of EEG were normal in 5 cases. The findings of neurologic evaluation were normal in 25 cases, and neuropsychiatric evaluation did not reveal any learning or behavioral problems in 22 cases.

compared with ideal weight occurred in 10 patients (26.3%) within the first 3 months of the study; after 24 months, this adverse effect occurred in only 7% of patients. In no case of weight gain it was necessary to suspend drug treatment. Hormone levels (thyroid hormones, growth hormone, cortisol) did not show any pathologic changes. An increased risk of asymptomatic visual field constriction may be associated with vigabatrin treatment. In the affected patients, the treatment was discontinued, and the ophthalmological tests will be repeated at 6 months (work in progress).

CARBAMAZEPINE GROUP

Regarding clinical efficacy, 7 relapses (21.9%) occurred: 5 within the first 6 months of the study and the other 2 after 1 year. Two patients were treated with vigabatrin monotherapy and became seizure free. Five patients received carbamazepine plus add-on therapy with another antiepileptic drug (vigabatrin in 3 of the 5 patients). Complete control was achieved in 1 patient (who was receiving both carbamazepine and vigabatrin). All 5 patients were excluded from the study. The epilepsy was symptomatic in 4 cases, cryptogenic in 2 cases, and idiopathic in 1 case. The EEG did not show any significant changes.

The adverse effects were excessive sedation in 6 patients, weight increase in 3 patients, and urticarial rash within the first 10 days of therapy in 6 patients (18.8%). One of these 6 patients presented with a generalized urticarial rash and a persistent, very high fever, associated with serious leukopenia (white blood cell count, 1.2 × 10^9/L). Carbamazepine therapy was suspended only in patients with skin rash. In the patient with serious leukopenia, the fever disappeared 24 hours after carbamazepine therapy was discontinued. The urticarial rash improved after 2 days, and disappeared after 5 days. The white blood cell count was 5.4 × 10^9/L after 5 days. Serologic tests were negative for antibodies against Epstein-Barr virus, cytomegalovirus, and Toxoplasma gondii.
A large proportion of childhood epilepsies are partial epilepsies. The presence of idiopathic epilepsy, typical of this age group, makes the prognosis quite favorable, but a high frequency of seizures at onset can make treatment difficult. Many drugs can provide effective therapeutic control, but current studies are aimed at identifying a regimen that offers minimal risk of serious adverse effects, minimal interference with cognitive functions, and minimal disruption to interpersonal relationships.

Comparison of the 2 groups of patients in the present study demonstrated that the clinical efficacy of vigabatrin is similar to that of carbamazepine (76.3% vs 78.1%, respectively). In both groups, relapses occurred mainly in patients with symptomatic epilepsy.

Regarding adverse effects, vigabatrin therapy resulted in a higher incidence of significant weight increase than previously reported for children in the literature. This weight gain, apparently, does not depend on metabolic or hormonal alterations, but seems to be due to an increase in appetite. The altered eating pattern does tend to stabilize with time, and therapy was not discontinued in any patient exhibiting weight increase. With carbamazepine therapy, skin rash was a significant adverse effect and in 1 case was associated with serious leukopenia. The other adverse effects were not considered clinically important.

Therapeutic efficacy was stable during follow-up. We believe that vigabatrin can be considered as equally suitable as other traditionally used drugs for the treatment of patients with newly diagnosed partial epilepsy. Therapeutic efficacy is comparable with that of carbamazepine. Two patients in whom relapses occurred early with carbamazepine therapy were subsequently treated with vigabatrin and have been seizure free over the 2-year follow-up period. The adverse effects of vigabatrin are of slight clinical account. Further comparative studies evaluating the cognitive and behavioral effects of the various antiepileptic drugs will define more clearly the role of vigabatrin in the complex treatment of the young patient with epilepsy.

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Reprints: Nelia Zamponi, MD, Department of Pediatric Neurology, “G. Salesi” Children’s Hospital, Via Corridoni, 11, 60 123, Ancona, Italy.

REFERENCES