ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN—POLONIA
VOL. LVI, 6 SECTIO D 2001

Department and Clinic of Neurology, Medical University of Lublin

BARBARA CHMIELEWSKA, ZBIGNIEW STELMASIAK

Clinical evaluation of Gabitril and Lamictal for drug-resistant epilepsy in adults

Lamotrigine (Lamictal ®, LTG) and tiagabine (Gabitril ®,TGB) are next new antiepileptic drugs (AEDs) to be marketed in the last years (4,12). They are licensed for adjunctive treatment of both simple and complex partial seizures (PS) with or without secondary generalisation that are poorly controlled by conventional first-line regimens (5,9). Placebo-controlled clinical studies of both LTG or TGB are generally powered to determine similar reduction in seizure frequency. On the other hand only occasional comparative-drug trials have been done and they constituted not the same profile of LTG v. TGB tolerability (3). Although seizure frequency is the common outcome index used to determine efficacy of new AEDs, there is a need for a border range of evaluation to assess the overall therapeutic benefit of the treatment as the quality of life with epilepsy is nowadays the target goal of management (7,15). The measurement of patients' self-esteemed well-being provides the clinician greater sensitivity as to a patient's response to treatment and may be helpful when choosing therapeutic regimen.

The aim of this investigation was to assess: 1) efficacy and tolerability of LTG or TGB as add-on treatment in patients with refractory complex partial seizures (CPS) with or without generalisation using a physician-rated measures and 2) patient-perceived change in the quality of life by the use of descriptive estimation and visual analogue scale (VAS).

METHODS

S t u d y d e s i g n . One-centre, prospective, open, placebo uncontrolled clinical trial in refractory CPS patients randomised to either LTG or TGB as add-on treatment.

T r e a t m e n t s e q u e n c e

- baseline: weeks from (-)12 to 0 (stable doses of baseline medication)
- titration: weeks from 1 to 8 (LTG dose built from 25 to 400 mg/d:1-2x, TGB – 5 to 60 mg/d: 3x)
- evaluation: weeks from 9 to 20 (stable for individual patients doses of LTG or TGB).

P a t i e n t s

Inclusion criteria: 1) adults aged 16-60 years, 2) CPS in accordance with ILAE* classification, 3) refractory epilepsy during at least 1 year and 4 or above CPS/ 4 weeks

during the last 3 months, 4) intake of a maximum 2 concomitant AEDs, 5) ability that all seizures be recorded in a seizure diary throughout the trial.

Exclusion criteria: 1) data of status epilepticus during the last year, 2) any signs of serious somatic or psychiatric pathologies, 3) data of non-compliance during previous treatment.

Evaluation

Efficacy: 1) changes in seizure frequency were calculated for each patients by comparing the difference between the monthly rate during a baseline and after evaluation phase, 2) response rate – percentage of patients with > 50% reduction of seizure frequency (so-called responders).

Tolerability: 1) percentage of patients with at least one treatment emergent adverse event, 2) laboratory values: standard haematology and clinical biochemistry.

Quality of life: 1) VAS -100 mm visual analogue scale : 0 mm – the worst, 100 mm – the best well-being assessed by a patient, 2) descriptive terminology scale of illness severity: 0 – absent, 1 – mildly, 2 – moderately, 3 – severely expressed symptoms.

Statistics. Differences from baseline in test response was compared at add-on phase using the Wilcoxon test. p-value < 0. 05 was considered statistically significant.

RESULTS

Efficacy (Table 1, Fig. 1, Fig. 2). In clinically-matched groups there was a significant, similar reduction in seizure frequency both after LTG and TGB expressed respectively as 41 and 35% responder rate as compared with baseline. In about half of patients in both groups no perceived improvement was noted.

Comparable was also the percentage of seizure-free patients during add-on phase (about 8%).

Table 1. Demographics

	LTG	TGB	
N	22	26	P. value
Gender : male (%)	59.01	53.85	
Age (y) – Mean (SD)	25 (6.7)	27(8.2)	
Epilepsy duration (y) – Mean (SD)	10 (7.1)	11 (8.2)	0.16 – 0.48
Aetiology – unknown (%)	81	85	
Seizure frequency at baseline (monthly)	7.18	6.89	
Dosage during evaluation – Mean (SD) (mg/d)	378 (53)	43 (14)	

Tolerability (Tab. 2, Fig. 3). Fewer patients in LTG group (23%) compared to TGB (35%) reported any adverse (AE) event during treatment. Most frequent AE in LTG group were headache, dizziness, disturbed sleep (loss of sleep), nervousness. In TGB-treated patients the commonest complains were: fatigue, headache, somnolence, dizziness and nausea. Disturbances disappeared spontaneously and there were no discontinuations due to AE in both groups. Laboratory values did not show any clinically relevant changes.

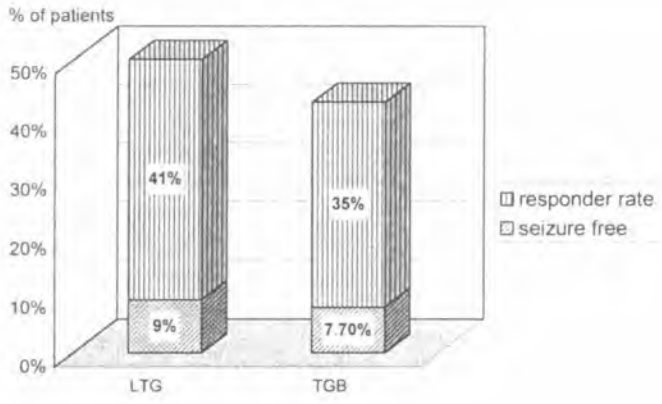

Fig. 1. Responder rate and seizure-free patients

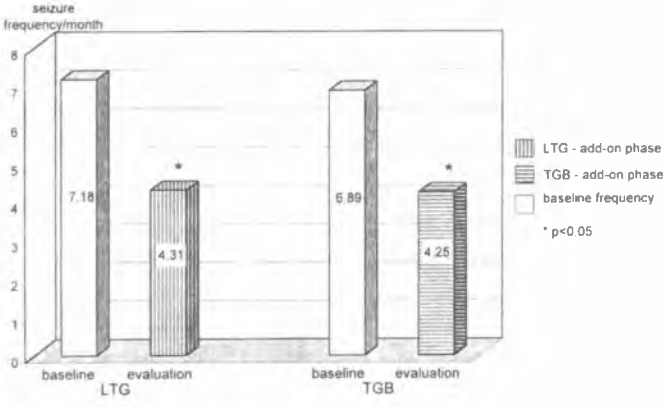

Fig. 2. Median monthly seizure frequency

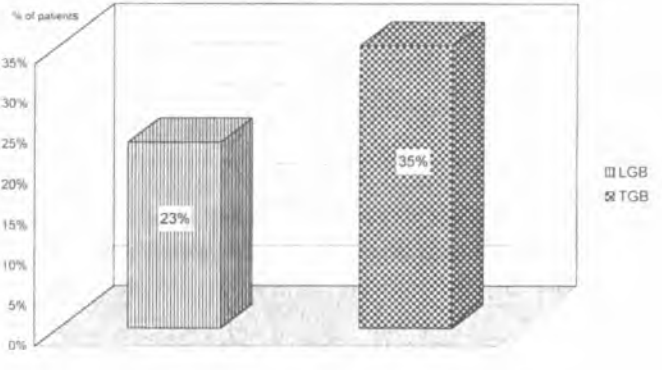

Fig. 3. Patients with at least one treatment – relevant adverse event

Table 2. Most common treatment – emergent adverse events*

Adverse Event	% Patients	
	LTG	TGB
Headache	27. 2	30. 7
Fatigue	22. 7	34. 6
Disturbed sleep	18. 2 (loss of sleep)	26. 9 (somnolence)
Dizziness	18. 2	23. 7
Nervousness	22. 7	3. 9
Paresthesia	13. 6	11. 5
Nausea	9. 0	15. 4
Flu syndrome	9. 0	7. 7
Rash	4. 6	0. 0

* Cumulative incidence>10% in either group.

L i f e s a t i s f a c t i o n. Descriptive terminology scale (Fig. 4). When about $^{3}/_{4}$ of patients scored their seizure as severe, it diverted to above $^{1}/_{2}$ of the group after TGB add-on. It was similar in LTG patients: 2/3 of severe esteems changed to less than $^{1}/_{2}$. There were also not visible differences in positive esteems (moderate or mild fits) between LTG and TGB (diversion from 32 to 56%, and from 27 to 46%, respectively).

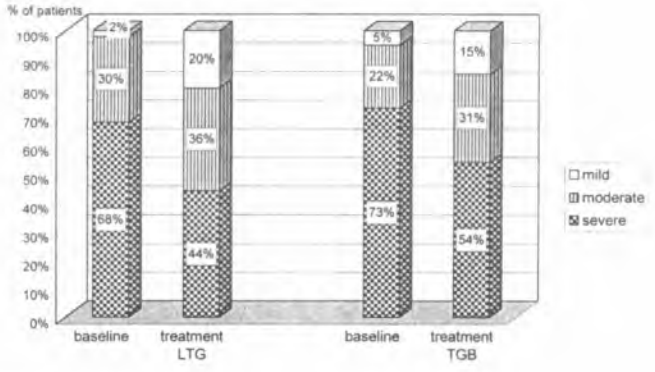

Fig. 4. Change in descriptive terminology scale of seizure severity

VAS (Fig. 5). Well-being coefficient was significantly greater in LTG but not TGB add-on phase; the distinction of the LTG-patients life satisfaction showed a peak at around 69 mm by the VAS as compared with 27 mm at baseline. TGB patients also recognised some improvement, but unmarked.

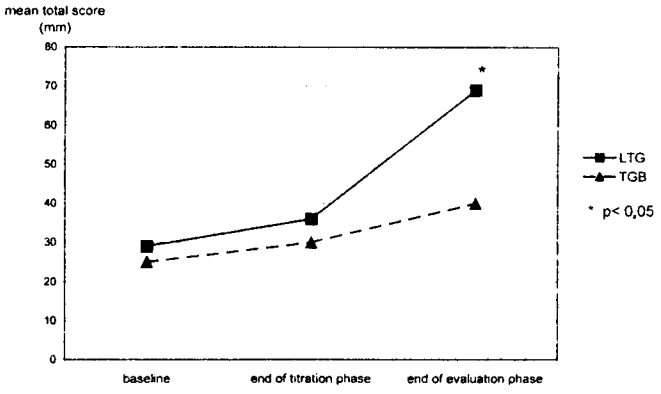

Fig. 5. Change in visual analogue scale

DISCUSSION

Patients with epilepsy often suffer not only physical, but also psychological and social handicaps which impair their quality of life (2, 6). The physical symptoms which contribute to these handicaps include the severity of epileptic fits (frequency, intensity) and the side effects of treatment (2). Both seizure frequency and adverse events are the most common measures used by clinicians to evaluate efficacy of treatment. While they are important determinants of the intensity of the patients epilepsy and the efficacy of the new medication, they do not directly assess the patients overall experiences. Seizures frequency, type and severity independently contribute to patients quality of life. Satisfaction with treatment may be connected not only with quantity but also with the quality of side effects and required therapeutic schedule (11,14). Although most literature data confirm similar percentage of patients suffering from LTG or TGB side effects which are mainly non-specifically neurotoxic, LTG exerts rather stimulatory, mood-elevating effects, while TGB is mainly sedative and even neurodepressive (1, 7, 8). Once a day intake of LTG resulting from its profitable pharmacokinetics enhances comfort of treatment and positively influences patient's compliance which may be essential for the final therapeutic effects (3). As these influences create patient's subjective estimations of living with epilepsy and its management it may be more essential to include differential QOL tests than choosing proper drug for add-on therapy among several new, comparatively effective. In our short-term observation reduction in seizure frequency, decreased seizure severity and improvement in patient's overall well-being did not entirely coincide. Visual analogue scale was in better accordance with objective measurement of treatment effectiveness (mainly tolerability), and revealed finer qualitative differences than descriptive terms (10, 13). Above all, the latest scale requires a significant time commitment for instruction and administration. However, it seems that two-tailed measurement of epilepsy outcome provides the clinician with more comprehensive information of the treatment effects.

Our preliminary observation concerning different overall efficacy of LTG and TGB as add-on treatment of partial seizures needs an additional assessment in long-term studies and with a greater group of patients.

CONCLUSIONS

1. LTG and TGB were similarly efficacious as add-on and short term treatment in refractory partial seizures.

2. Overall incidence of adverse events was greater after TGB; somnolence and fatigue were most frequently reported.

3. The positive impact on the quality of life was more particularly observed among LTG patients.

4. Comparable reduction in seizure frequency and severity after LTG and TGB did not entirely coincide with the improvement of patient's self-esteem ed quality of life.

REFERENCES

1. Aldenkamp A. P. et al.: Cognitive effects of lamotrigine as first-line add-on in patients with localisation-related (partial) epilepsy. J. Epilepsy, 10, 117,1997.
2. Baker A. et al.: Quality of life in people with epilepsy. A European study. Epilepsia, 38, 353, 1997.
3. Bialer M. et al.: Progress report on new antiepileptic drugs: a summary of the Third Eilat Conference. Epilepsy Res., 25, 299, 1996.
4. Boas J. et al.: Controlled trial with lamotrigine (Lamictal) for treatment resistant partial seizures. Acta Neurol. Scand., 94, 247, 1996.
5. Brodie M. J.: Tiagabine in the management of epilepsy. Epilepsia, 38 (suppl. 2), S23, 1997.
6. Cochrane H. J. et al.: Neuropsychological outcomes in randomised controlled trials of antiepileptic drugs. A systematic review of methodology and reporting standards. Epilepsia, 39, 1088, 1998.
7. Dodrill C. B. et al.: Cognitive and quality of life effects of differing doses of tiagabine in epilepsy. Neurology, 48, 1025, 1997.
8. Dodrill C. B. et al.: Effects of tiagabine monotherapy on abilities, adjustment, and mood. Epilepsia, 39, 33, 1998.
9. Fitton A., Goa K. L.: Lamotrigine: an update of its pharmacology and therapeutic use in epilepsy. Drugs, 50, 691, 1995.
10. Grunberg S. M. et al.: Comparison of conditional quality of life terminology and visual analogue scale measurements. Qual. Life Res.,5, 65, 1996.
11. Leach J. P, Brodie M. J.: New antiepileptic drugs: an explosion of activity. Seizures, 4, 5, 1995.
12. Leach J. P., Brodie M. J.: Tiagabine. The Lancet, 351, 203, 1998.
13. Norrby V. et al.: Self-assessment of well-being in a group of children with epilepsy. Seizure, 8, 228, 1999.
14. Perucca E.: The new generation of antiepileptic drugs: advantages and disadvantages. Br. J. Clin. Pharmacol., 42, 531, 1996.
15. Rossinyol A. et al.: Changes in the quality of life of epileptic patients treated with lamotrigine. Epilepsia, 37(suppl. 4), 10, 1996.

2000.11.23

SUMMARY

Second generation antiepileptics lamotrigine (LTG) and tiagabine (TGB) were primarily licensed for adjunctive treatment of simple and complex partial seizures with/ without secondary generalisation as similarly effective drugs. Reduction of seizures frequency is the most important index of drug efficacy, but overall therapeutic benefit estimated as a quality of life is nowadays the target goal of management. In this study efficacy and tolerability of LTG or TGB as short-term add-on treatment in patients with refractory complex partial seizures were assessed by the use of both physician-rated measures (mean monthly seizure frequency, responders rate, adverse events, clinical biochemistry) and patients perceived change in their own quality of life estimation (descriptive scale and visual analogue scale-VAS). Comparable efficacy of LTG (n-22, 378 mg/day) and TGB (n-26, 43 mg/g) was assessed as 41 and 35% of responders and above half of patients with noticeable improvement. 25% of patients in both groups reported reduction of seizures severity in 4-points descriptive scale. Biochemistry values did not show clinically significant changes after treatment. 13 % of patients on LTG reported adverse events (headache, asthenia, irritability, insomnia). This coefficient was greater for TGB – 35% (asthenia, headache, sleepiness, vertigo). However, no case of discontinuation as a result of adverse events was reported for either of the tested drugs. Even if efficacy of LTG and TGB was comparable in objective measurements, only patients on LTG reported a significant quality of life improvement in VAS. This might be the consequence of more frequent adverse events and treatment schedule of TGB (triple dosing/day). This trial confirmed that VAS might be used as an easy additional test in evaluation of antiepilepic drug for individual patient in everyday clinical practice.

Ocena kliniczna efektywności Gabitrilu i Lamictalu w terapii dodanej padaczki lekoopornej u pacjentów dorosłych

Lamotrygina i tiagabina należą do licznej grupy leków przeciwpadaczkowych nowej generacji, dla których istnieje podobne wskazanie do stosowania w leczeniu skojarzonym padaczek lekoopornych z napadami częściowymi złożonymi. Obecnie za skuteczną uznaje się terapię, która wpływa na poprawę jakości życia chorych nie tylko poprzez zmniejszenie ilości napadów przy dobrej tolerancji leczenia, lecz również poprzez brak negatywnych oddziaływań lub nawet poprawę w sferze funkcjonowania poznawczego, emocjonalnego i społecznego. W prezentowanej obserwacji porównano efektywność krótkoterminowej terapii dodanej LTG (śr. dawka -378 mg/ d) lub TGB (43 mg/ d) odpowiednio u 22 i 26 dorosłych z padaczką z napadami częściowymi, u których w dotychczasowym leczeniu nie uzyskano wystarczającej kontroli. Stwierdzono porównywalną skuteczność obu leków, tj. 41 i 35% responderów (> 50% redukcja miesięcznej liczby napadów) w grupie LTG i TGB oraz jednakowy odsetek – 50% chorych, którzy relacjonowali jakąkolwiek poprawę. Co najmniej czwarta część chorych w obu grupach stwierdzała znaczące zmniejszenie intensywności napadów, na podstawie czterostopniowej skali opisowej.* Nie stwierdzono klinicznie istotnych zmian w laboratoryjnych badaniach biochemicznych po leczeniu LTG i TBG. U 13% osób stosujących LTG wystąpiły objawy niepożądane: bóle głowy, zmęczenie, rozdrażnienie, bezsenność. Do najczęstszych objawów ubocznych u 35% chorych stosujących TGB należały: zmęczenie, bóle głowy, senność, zawroty głowy. Zaburzenia te były przemijające i w żadnym przypadku nie stały się przyczyną odstawienia leku. Pomimo podobnej skuteczności przeciwdrgawkowej obu leków jedynie pacjenci stosujący LTG relacjonowali istotną poprawę jakości życia w ocenie przy zastosowaniu skali wizualnej (VAS). Większa częstość objawów niepożądanych i mniej wygodny sposób dawkowania TGB (3-krotnie/dobę) mogły zaważyć na mniej

korzystnej ocenie przez pacjentów leczenia TGB w porównaniu z LTG. VAS może stanowić istotny dodatkowy test, pozwalający na wybór najwłaściwszego leku przeciwpadaczkowego dla indywidualnego pacjenta w terapii dodanej.

* Według klasyfikacji International League Against Epilepsy (1989).