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Long-term monotherapy with lamotrigine in newly diagnosed epilepsy in adults

Lamotrigine (Lamictal ®) (LTG) as both effective against a wide range of seizure types and epileptic syndromes and well-tolerated is nowadays an increasingly often used antiepileptic drug in a form of add-on treatment as well as in polytherapy with transition to monotherapy (2). Simultaneously, its role as a first-line therapy, also in a newly diagnosed epilepsy is extensively being evaluated. The mechanism of action of LTG in blocking the sodium channels in neuronal cell membranes and hence reducing the release of excitatory aminoacids, mainly glutamate, suggests that the compound might also negatively influence memory processes, learning abilities and cognition (1, 5). From the patient's point of view the influence of any drug on intellectual alertness is an important decisive factor in starting therapy and choosing one antiepileptic drug before other ones even if efficacy and tolerability is undoubtedly proved.

OBJECTIVE

The aim of the study was to determine the efficacy, safety and neuropsychological functioning after LTG treatment as long-term monotherapy in adults with recently diagnosed epilepsy.

METHODS

Into an open, non-comparative, 12 months' observational study, 24 young adults were included, aged between 17 and 34 years (mean: 22.5) and with newly diagnosed, cryptogenic and not previously treated epilepsy. Inclusion criteria were restricted to patients with normal intellectual level, and without other neurological disability or progressive disorder as well as without hepatic, renal and haematological abnormalities at baseline.

After three months' observational period necessary for estimation of baseline frequency of seizures, biochemistry parameters and psychological data LTG was titrated for at least 6 weeks from 25 to 500 mg/day (mean 316 mg/day) and administered for up to 12 months as divided into two doses/day.

Efficacy was evaluated as a proportion of patients with at least 50% reduction of seizure frequency

from baseline. Occurrence of adverse events was scored in every three-months treatment periods. Mean values of basic biochemical laboratory parameters estimated every three months were: haematology, ALT, ASP, GGTP, alkaline phosphatase, total bilirubin, protein, cholesterol, triglycerides, glucose, electrolytes, urea, uric acid and creatinine.

Initial parameters of evoked potentials: visual (VEP; P100 latency), brainstem (BAEP I-II, I-IV interlatency), event-related (ERP/P300) and blink and masseter reflex were reassessed after 12 months of monotherapy.

In patients after evaluation of a psychological profile by the use of MMPI (Minnesota Multiphasic Personality Inventory) cognitive functioning in Benton Visual Retention Test, Bender Visual Perception Test, Auditory Verbal Learning Test, selected battery from Łuria- Nebraska and Wechsler-Bellevue Intelligence Scale performed at baseline were reestimated after six and twelve months of LTG treatment.

Statistical analysis was performed by the use of Student's - t and Wilcoxon tests. Values of $p < 0.05$ were considered significant.

RESULTS

Seizure frequency (Fig.1). A total of 67% of patients experienced improvement throughout the LTG treatment period, i.e. at least 50% reduction in seizure frequency from baseline. The proportion of patients who were seizure-free equalled 42%. The best were the results in patients with generalized tonic-clonic seizures (GCTS) – 87% were seizure-free. Poor efficacy occurred in general non-convulsive seizures (GNCS) (25% improved).

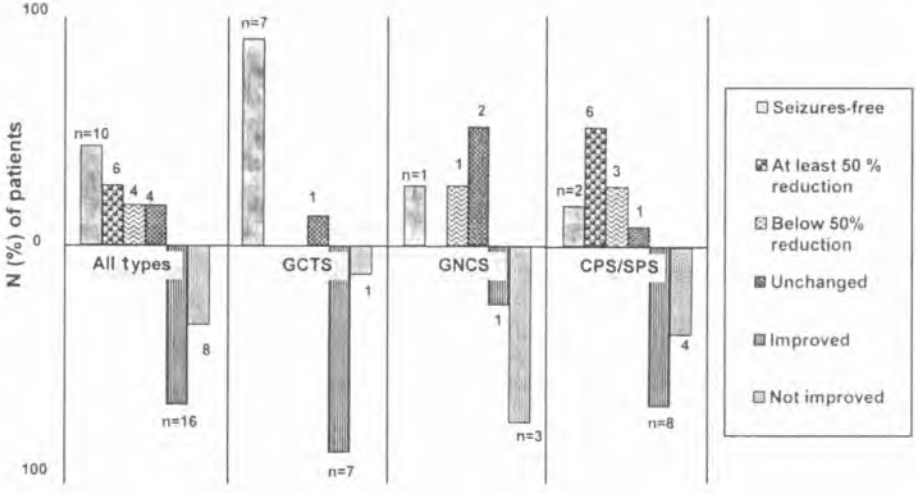

Fig. 1. Effect of lamotrigine on seizure frequency

Adverse events (Fig. 2). The proportion of patients who experienced adverse events during observational period decreased gradually from 5 (21%) over the first 3 months to 1 (4%) at the end of exposure. The complaints were mainly neurotoxic in their characteristics; the most common were headaches (12%) and asthenia (8%). They did not influence the discontinuation of treatment. There were no cases of rash.

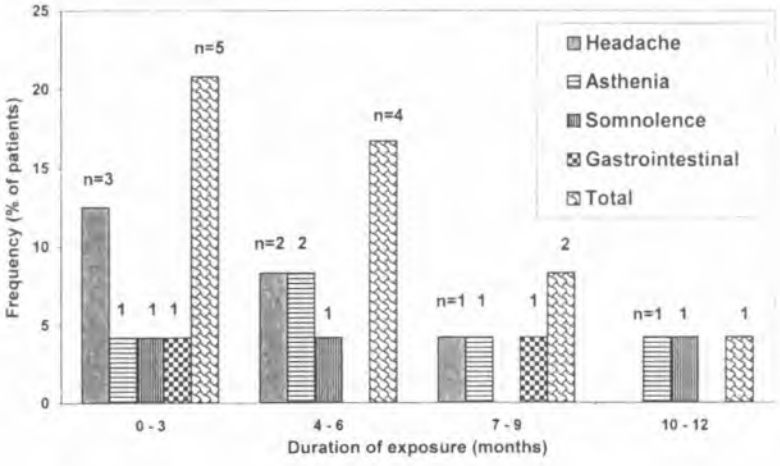

Fig. 2. Adverse events during lamotrigine therapy

Clinical biochemistry (Fig. 3). There was nether clinically significant influence of LTG on hepatic and renal parameters nor on the most of haematological values during the whole treatment period. Statistically significant decrease of lymphocytes count and volume of erythrocyte (MCV) after 9 and 12 months still covered the lower level of physiological range.

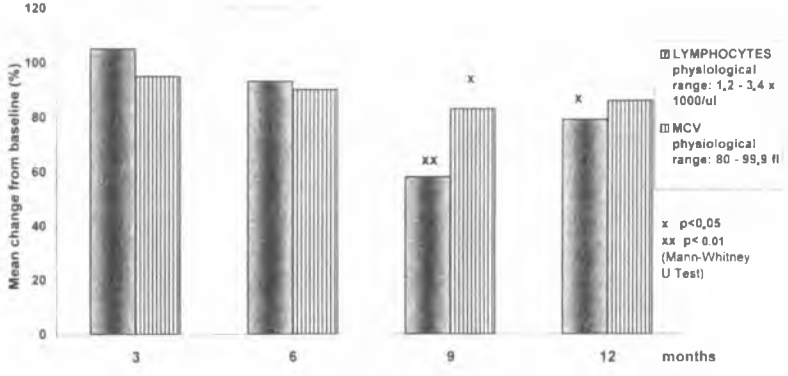

Fig. 3. Statistically significant changes in haematological values during lamotrigine monotherapy

Neuropsychological testing

Auditory Verbal Learning Test – mean amount of three consecutive repetitions of 10-word-list did not change from baseline level after 6 and 12 months of LTG treatment; a rise from 6.8 repetitions up to 8.0 and 8.6, i.e. up to117 and 126% after 6 months, and from 6.8 up to 7.8 and 8.1 or 115 and 118% after 12 months.

Direct Visual Memory Test – (exposing of 6 pictures) revealed the constant proportion of patients (21%) with difficulties during the course of observation as a consequence of some neurodynamic disturbances.

The proportion of patients with organic deficits and neurodynamic difficulties remained at the same level after 6 and 12 months. Focal disturbances of frontal and temporal origin were more common after 12 months (Fig. 4).

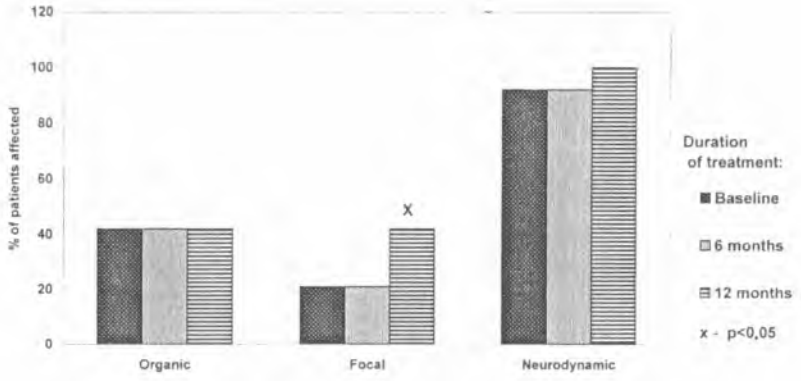

Fig. 4. Organic, focal and neurodynamic disturbances in neuropsychological examination during lamotrigine monotherapy

Testing of abstractive and operative thinking processes revealed a greater number of patients with difficulties after 12 months (Fig. 5).

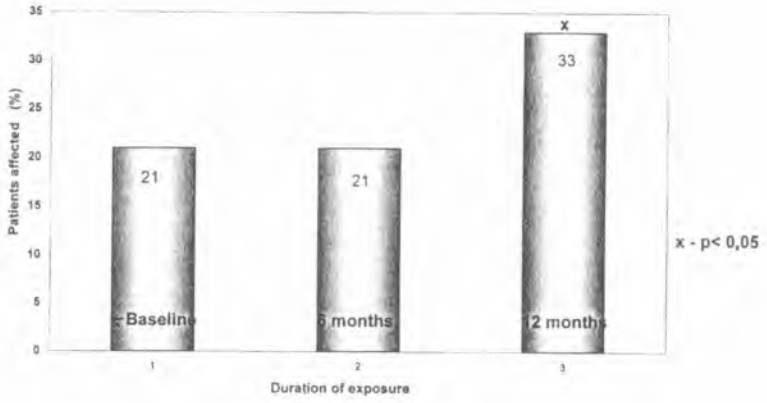

Fig. 5. Testing of abstractive and operative thinking process

Neurophysiological examinations. No significantly changed parameters between baseline and post-treatment evaluation of VEP, BAEP, ERP, mSEP and BR were noted. The only results of MR show significantly prolonged latency (Tab. 2).

Table 1. Characteristics of patients

Number of patients	**24**
Gender - F/ M	**16/ 8 (67%/ 33%)**
Age (years) : range; Mean (SD)	**17 – 34; 22.5 (7.2)**
Seizure types: complex v. simple partial (CPS/ SPS) primarily generalised tonic-clonic (GCTS) primarily generalized non-convulsive (GNCS)	**12 (50%)** **8 (33%)** **4 (17%)**
Baseline seizure frequency (n/per month): CPS/ SPS GCTS GNCS	**4. 25** **2. 25** **12. 25**
Doses of LTG ; mean; (range) (mg/ day) : all patients CPS/ SPS GCTS GNCS	**316 (200 - 500)** **274.8 (200 - 500)** **275 (200 - 350)** **400 (300 - 500)**

Table 2. EPs latencies and interlatencies during LTG monotherapy (msec)

	Baseline Mean SD	After treatment Mean SD
VEP/ P-300	105. 13 5. 67	105. 63 4. 03
BAEP/ I – III	2. 28 0. 15	2. 24 0. 18
BAEP/ I – V	4. 17 0. 18	4. 09 0. 15
mSEP/ CCT	6. 49 0. 44	6. 59 0. 30
ERP/ P- 300	290. 27 14. 59	314.15 15. 22
BR	10. 49 0. 60	10. 75 1. 1
MR	6. 90 0. 49	7. 48 0.83*

* $p>0.05$.

DISCUSSION

Among a large number of newer generation antiepileptic drugs only two of them – lamotrigine and oxcarbazepine have so far been licensed for use as monotherapy and only in adult patients. Although lamotrigine appears to be particularly effective not only for partial but also against generalized tonic-clonic seizures and specific epileptic syndromes like a Lennox-Gastaut it is still not recommended as first line monotherapy until further studies are done (1, 5).

In our one-year observational study in a small group of young adults with *de novo* diagnosed epilepsy LTG as a first-choice monotherapy appears to be both effective and well tolerated. A total of 67% of patients responded to therapy that means at least 50% reduction seizure frequency per month and 42% of them were completely seizure free. According to seizure type the best results were in patients with generalized convulsive seizures as 87% of them stayed seizure-free during observational period. Good effectiveness was also observed in patients with partial seizures; distinct control of seizures was noted in 2/3 of the group. Only patients with generalized non-convulsive fits did not respond effectively to LTG even if higher doses of drug were used. However, the last observation may be the result of a small proportion of patients in this sub-group. In previous few studies the drug has also shown distinct protection against absence, atonic and myoclonic seizures (4, 5). Generally our results with LTG efficacy are in agreement with an established opinion concerning the so-called standard drugs that about 60% of patients respond to initial therapy, irrespective of the drug used. So they might also confirm the usefulness of LTG as next antiepileptics of the first choice in monotherapy of partial and generalized convulsive seizures (11, 12). Clinical efficacy of LTG against partial and generalized tonic-clonic seizures has been established in numerous clinical trials as being similar to that of first-line therapies with carbamazepine or phenytoin; according to addiction of LTG in doses between 50 and 500 mg/day, above 50% protection may be achieved in 7 to 67% of refractory epileptic patients (5, 8).

As monotherapy in adults with newly diagnosed epilepsy, 100 to 300 mg/day of LTG have been confirmed similarly effective to carbamazepine or phenytoin against partial or generalized convulsive seizures but simultaneously it has been better tolerated (3, 14, 15). The most common adverse effects of LTG are usually neurological, gastrointestinal and dermatological, and among the most frequent are headaches, asthenia, skin rush, nausea and disturbed sleep; these are noted in about 8-20% of patients (3, 15). This was also observed in actually tested patients; 21% of them complained mainly of mentioned above neurotoxic or gastric disturbances in the initial period of treatment, although no case of skin reaction was reported. Even if the mean doses of LTG applied in this observation were a little above the quoted levels these initial adverse reactions diminished in the course of treatment without any case of withdrawal from therapy. Good tolerability of LTG in the presented observation was also stressed by its minimal influence on majority of biochemical parameters tested in long term treatment. Decrease in both lymphocytes count and mean erythrocyte dimension observed after 12 months' treatment still covered the lower level of physiological range. These were no longer confirmed during continuation of LTG after observational period, however in lower doses. Lamotrigine was developed with the intent to take advantage of its antifolate properties in controlling seizure activity. However, its weak antifolate activity seems to exert little or none antiseizure action and probably produces no clinically significant alteration in haematological parameters or just in a restricted group of predisposed patients (9, 10). It is postulated that some of them might be recognized during haematological testing before the planned treatment (9). Changes in white cells count and some biochemical parameter were rather seen in patients during long-term treatment when LTG was added to carbamazepine or phenytoin (8)

Even if we did not find disturbances in auditory verbal learning test and direct visual memory test

and the proportion of patients with neurodynamic difficulties and organic deficits stayed at the same level after one-year treatment with LTG, the explanation of increased proportion of patients with difficulties in abstractive and operative thinking processes is not entirely clear, particularly if noted moderate focal deterioration was predominantly of frontal or temporal localization, which was in agreement with electroencephalographic as well as clinical signs of seizure origin in the observed patients. These changes in neuropsychological testing that might result both from LTG treatment and epilepsy course needs more detailed insight in future studies. However, it is just worth stressing that evoked potential parameters and especially P-300 latency, mostly suggestive for cortical arousal and cognitive processes did not change in the course of prolonged LTG treatment (7). On the other hand, several studies have demonstrated that LTG when used in therapeutic range did not impair cognition and psychomotor function, either in healthy volunteers or in patients with intractable epilepsy in comparison with conventional and some newer antiepileptic drugs like carbamazepine, phenytoin or vigabatrin (2, 6, 9). In a study of Smith's directly comparing LTG to placebo no cognitive effects were observed in a limited neuropsychological battery and in other ones favourable effects of LTG on psychological well-being were not explained simply by decrease in seizure frequency and severity, but might be secondary to positive mood effects of LTG (13). LTG is a novel antiepileptic drug that may possess unique psychotropic profile. More extensive neuropsychological studies will determine possible favourable behavioral effects of LTG for patients with epilepsy.

CONCLUSIONS

1. Introduction of lamotrigine as a monotherapy in young adults with newly diagnosed epilepsy appeared to be associated with a distinct reduction in seizure frequency.

2. Treatment with lamortigine did not influence a number of the laboratory parameters and haematological changes were of limited clinical significance.

3. Moderate adverse event, in the initial period, predominantly affected the central nervous system, but without necessity of withdrawal

4. Battery of evoked potentials, and especially P300, did not change during the course of treatment.

5. There was no significant change in measures of neuropsychological examinations, but moderate increase in focal disturbances and exacerbation of abstractive thinking process is worth of re-evaluation in a controlled clinical trial whether it was a treatment or epilepsy consequence.

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SUMMARY

Lamotrigine (LTG) as both effective against a wide range of seizure types and epileptic syndromes and well tolerated drug is being used in mono- as well as in polytherapy of pharmacoresistant epilepsy. The aim of this study was to evaluate the efficacy, safety and neuropsychological functioning after LTG (mean daily dose: 316 mg) as long-term monotherapy (12 mo) in 24 young adult out-patients (22.5 ys) with newly recognised and not-previously treated epilepsy in an open, non-comparative trial. 67% of patients were responders (above 50% reduction in seizure frequency) and 42% reported seizures remission. The best were results in patients with generalised convulsive fits (87% with remission). Adverse events in the early phase of medication in 21% of patients typically concerned CNS and gastrointestinal system (headache, asthenia, insomnia, nausea, gastric aches) and resolved spontaneously without treatment discontinuation. Biochemical examinations were normal and transient leucopenia and diminishion of MCV were clinically not significant. Neurodynamic abilities, neuropsychological examination results, memory verbal and visual tests and organic evaluation in organic triada tests did not show deterioration after LTG treatment. Slight difficulties in abstractive and operative thinking and some focal symptoms of fronto-temporal origin should be considered a result of drug but also the epilepsy *per se*. No significant differences in latencies and amplitudes of evoked potentials (VEP, BAEP, SEP and especially ERP-300) were measured after LTG. Preliminary results obtained in this study supported good efficacy and tolerability and especially lack of unfavourable influence of LTG on neuropsychological functioning in young previously untreated patients with epilepsy.

Długoterminowa obserwacja stosowania lamotryginy w monoterapii u pacjentów z nowo zdiagnozowaną padaczką

Lamotrygina (LTG), wyjątkowo wśród leków przeciwpadaczkowych nowej generacji, jest brana pod uwagę do stosowania w monoterapii ze względu na skuteczność w licznych rodzajach napadów padaczkowych i dobrą tolerancję leczenia, potwierdzoną w terapii dodanej. Przedstawiona roczna otwarta obserwacja dotyczyła efektywności LTG stosowanej w średniej dawce 316 mg/ dobę oraz wpływu leczenia na tzw. wyższe czynności nerwowe w badaniach neuropsychologicznych oraz na potencjały wywołane (EP) u dotychczas nie leczonych 24 dorosłych pacjentów z nowo zdiagnozowaną padaczką kryptogenną, z napadami częściowymi lub uogólnionymi. U 67% pacjentów stwierdzono > 50% redukcję częstości napadów, a u 42% całkowitą ich remisję. Najlepszą reaktywność wykazywali chorzy z napadami uogólnionymi drgawkowymi (87% osób bez napadów). Objawy niepożądane stwierdzane w początkowym okresie leczenia u 21% chorych typowo dotyczyły układu nerwowego i pokarmowego (bóle głowy, astenia, zaburzenia snu, zaburzenia gastryczne) i uległy zmniejszeniu do 4% badanych, nie sprowadzając w żadnym przypadku konieczności odstawienia leku. Nie stwierdzono istotnych zmian większości parametrów biochemicznych, a umiarkowana leukopenia i zmniejszenie MCV po 9 miesiącach stosowania LTG nie miały znaczenia klinicznego. Badania neuropsychologiczne z oceną funkcji pamięciowych w testach werbalnych i wzrokowych nie ujawniły zaburzeń pod wpływem leczenia, podobnie jak nie obserwowano nasilenia wyjściowych zaburzeń neurodynamicznych, jak również zmian w testach organicznych. Pacjenci wykazywali natomiast umiarkowane trudności w sferze myślenia operacyjnego i abstrakcyjnego, a ponadto ujawniono umiarkowane zaburzenia ogniskowe o lokalizacji czołowej i skroniowej, co może mieć związek zarówno z terapią, jak i ze schorzeniem *per se*. Nie stwierdzono istotnych zmian latencji i amplitud EP (VEP/ P100, BAEP, mSEP), a zwłaszcza ERP/ P300, którego zmiany zwykło się zwłaszcza łączyć z reakcją wzbudzenia w OUN i procesami poznawczymi. Przeprowadzona obserwacja potwierdza wysoką skuteczność i dobrą tolerancję stosowania LTG w monoterapii, w tym zwłaszcza brak niekorzystnego wpływu leczenia na funkcje psychiczne, także poznawcze, co jest istotnym problemem w leczeniu padaczki, szczególnie u rozpoczynających leczenie młodych pacjentów.