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Lamotrigine in Parkinson's disease – a double blind study

Short Communication

F. Zipp, F. Bürklin, K. Stecker, H. Baas, and **P.-A. Fischer**

Department of Neurology, University of Frankfurt/Main, Federal Republic of Germany

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Summary. Antiglutamatergic acting substances are considered to be useful tools for the treatment of hypokinesia in animal models for Parkinson's disease (PD). Moreover, most known antiglutamatergic compounds act postsynaptically and are either toxic or weak with regard to their clinical potency. The antiepileptic drug "Lamotrigine (LTG)" inhibits presynaptic glutamate release and may therefore provide a novel approach for PD therapy. Encouraging results from a pilot project led us to establish a placebo controlled trial including 20 patients with PD. The substance was generally well tolerated. There was a significant difference in the investigator's overall assessment of efficacy ($^{6}/_{10}$ vs. $^{2}/_{10}$ improvement; $p < 0.05$) and a tendency for LTG to exhibit a beneficial effect in some registration parameters, but no significant differences in motor response were found between the two groups. We failed to confirm that LTG mediates a strong antiparkinsonian effect in this small study, but to clearly demonstrate slight or moderate beneficial effects larger groups are required.

Keywords: Glutamate, glutamate release, antiglutamatergic activity, excitatory neurotransmitter, Lamotrigine, Parkinson's disease, basal ganglia, neurotransmission, therapy.

Introduction

Most therapeutic strategies in Parkinson's disease (PD) focus on direct or indirect stimulation of dopamine (DA)-receptors by L-dopa or DA-agonists. Despite the clinical benefits the use of such compounds is associated with several side effects and the efficacy is lost as the disease progresses. Thus, there is clear need to develop strategies based on different pharmacological principles. Recent animal experiments have demonstrated that antiglutamatergic activity has antiparkinsonian effects (Clineschmidt et al., 1982; Carlsson, 1993; Carlsson and Carlsson, 1989a,b, 1990; Löschmann et al., 1991;

Klockgether and Turski, 1989, 1990; Klockgether et al., 1991). The rational basis for an antiglutamatergic therapy in PD has been reviewed extensively with regard to the complex motor "circuitry" of the basal ganglia (Albin et al., 1989; Alexander et al., 1986, 1990; DeLong, 1990; Riederer et al., 1991).

The effects of various antiglutamatergic agents have been investigated in animal models of PD. Among these several N-methyl-D-aspartate(NMDA)-antagonists such as MK801 and 3-3(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid (CPP) showed marked locomotor-stimulating effects (Clineschmidt et al., 1982; Carlsson and Carlsson, 1989a) and provided some protection against the induction of nigrostriatal neuron degeneration (Turski et al., 1991). In addition NMDA-antagonists as well as the α-amino-3-hydroxy-5-methyl-4-isoxazole propionate(AMPA)-antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline (NBQX) showed functional synergism with dopaminergic substances (Carlsson and Carlsson, 1989b; Klockgether and Turski, 1990; Klockgether et al., 1991; Löschmann et al., 1991). However, the general toxicity of these compounds excludes most NMDA-antagonists as therapeutic agents in PD. The NMDA-antagonist amantadine is the only established therapy for clinical use, but unfortunately exhibits only a weak therapeutic potency.

The present study focussed on investigating the therapeutical potential of Lamotrigine (3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-triazine) [LTG], which inhibits the presynaptic release of glutamate- and aspartate by blockade of voltage-sensitive sodium channels and stabilisation of neuronal membranes (Leach et al., 1991). The pharmacology of LTG is well established (Cohen et al., 1987; Peck, 1991; Binnie et al., 1986; Posner et al., 1991), and it is generally used as an anticonvulsant. LTG is well tolerated, and the minor clinical side effects, such as dizziness, diplopia, somnolence, headache, ataxia, asthenia, nausea, and skin rashes, which have been reported are reversible (Betts et al., 1991).

After encouraging results in a preceding open pilot study (Zipp et al., 1993) it was the aim of this trial to evaluate under controlled conditions whether or not LTG has any beneficial effects on clinical symptomatology of PD.

Patients and methods

Twenty patients with advanced idiopathic PD were entered into the study, all of whom were suffering from late motor complications, such as loss of drug-efficacy, fluctuations and/or dyskinesias. Their ages ranged from 36 to 70 years, Hoehn & Yahr scores from 2 to 4, the duration of the disease from 6 to 26 years. All patients were treated in our outpatient clinic and were kept under stable anti-Parkinson medication for at least 30 days before entering the study. Patients with history of disorientation, mental confusion, marked dementia or other major psychic alterations were excluded.

The study was carried out under double-blind conditions. After group randomization all patients were assigned to either of the treatment arms (10/10). The study medication was applied as an add-on therapy to the otherwise unchanged prestudy medication.

The initial dosage of LTG was 50 mg/day which was then raised in 50 mg steps up to 200 mg/day on a weekly basis. The dosage was further increased at two week intervals to 200 mg/day, 300 mg/day and 400 mg/day respectively. It was then maintained of 400 mg/day for 3 months. This titration regimen was modified giving a lower dosage if an individual

patient achieved satisfactory motor improvement at submaximal doses or dose related side effects occured.

Standardized clinical ratings were performed regularly when the LTG dosage was increased and after each modification of the dosage, using the Columbia University Rating-Scale (CURS), measurements of gait velocity (2 × 10m) and the Purdue-Peg-board (25pins) to determine the motor disability.

The data were evaluated by calculating a global score and several subscores from the CURS. Fluctuations/dyskinesias were rated using a special scale (6pts. scaled, 9 items). Patients were asked to keep an hourly log of their actual mobility during the 7 days before each examination. Sleep-disturbances and other subjective complaints were registered as they were spontaneously reported by the patients, but also using a standardized questionnaire (16 items). The rating was completed by an investigator's assessment of the overall efficacy (5pts. scaled).

Blood pressure, heart-beat-rate, electrocardiogram, and standard laboratory data as well as γ-glutamyl-transferase were performed every 2 weeks during the titration period and monthly thereafter. All laboratory data were reviewed by a non-blinded external physician. At entry a chest x-ray was required from every patient.

Criteria for withdrawal from the trial were moderate or severe drug toxicity or other marked adverse reactions, rapid progression of clinical disability or protocol failures.

Statistical analysis for significancies was performed by using Student's t-test and multifactorial analysis of variance (ANOVA). Because of the number of drop-outs (see below) the statistical evaluation was only performed on the data obtained during the first 5 examinations. All other data were evaluated only on a descriptive level. All basic data, such as sex and disease duration, were tested for general association by use of the chi-square test.

The study was conducted in accordance with the revised Helsinki declaration and approved by the local ethical committee; before starting the trial all patients had given their written informed consent.

Results

The two groups were comparable with respect to their basic data. The values for the LTG vs. placebo groups were: age at PD-onset, 61.2 ± 5.3 and 54.1 ± 8.9 years; disease duration, 14.3 ± 6.4 and 11.3 ± 5.2 years; L-dopa treatment duration, 13.7 ± 5.4 and 10.3 ± 3.2; actual L-dopa dose, 645.0 ± 231.8 and 625.0 ± 234.8mg/day; Hoehn and Yahr stage, 2.8 ± 0.9 and 2.6 ± 0.5pts.; CURS global scores at entry, 26.9 ± 8.7 and 27.5 ± 7.3pts.. All patients were kept on selegiline. The two divisions differed — but not significantly — with respect to gender (LTG-group male/female 9/1, placebo group 6/4).

No serious adverse reactions were observed in either group. Side effects were transient and minor in all patients. Two patients in the LTG vs. 1 in the placebo-group complained of headache and 2 vs. 0 of vertigo. Palpitations were mentioned by 1 patient and abnormal sweating by 2 patients in the placebo-group, but were not existing in the verum-group. The overall incidence of undesired side effects was very low in both groups.

6 patients, 4 in the LTG- and 2 in the placebo-group, dropped out of the trial for different reasons. In the LTG-group 2 patients denied to continue due to a subjective increase of akinesia. The third LTG-patient discontinued the medication after a traumatic humerus-fracture. Up to this event he had shown an increase in dyskinesias. The fourth LTG-patient stopped the trial because of unspecified subjective discomfort and despite an improvement of his motor condition. Minor depressive disorder had been known in this patient for

several years. In the placebo-group 2 patients refused further participation due to a lack of motor improvement.

Figure 1 shows the CURS global-score and the various CURS-subscores. The clinical course was almost identical in both groups. As far as the statistical evaluation of the data could be accomplished there were no significant differences. However, at late examinations some subscores [wearing-off, gait

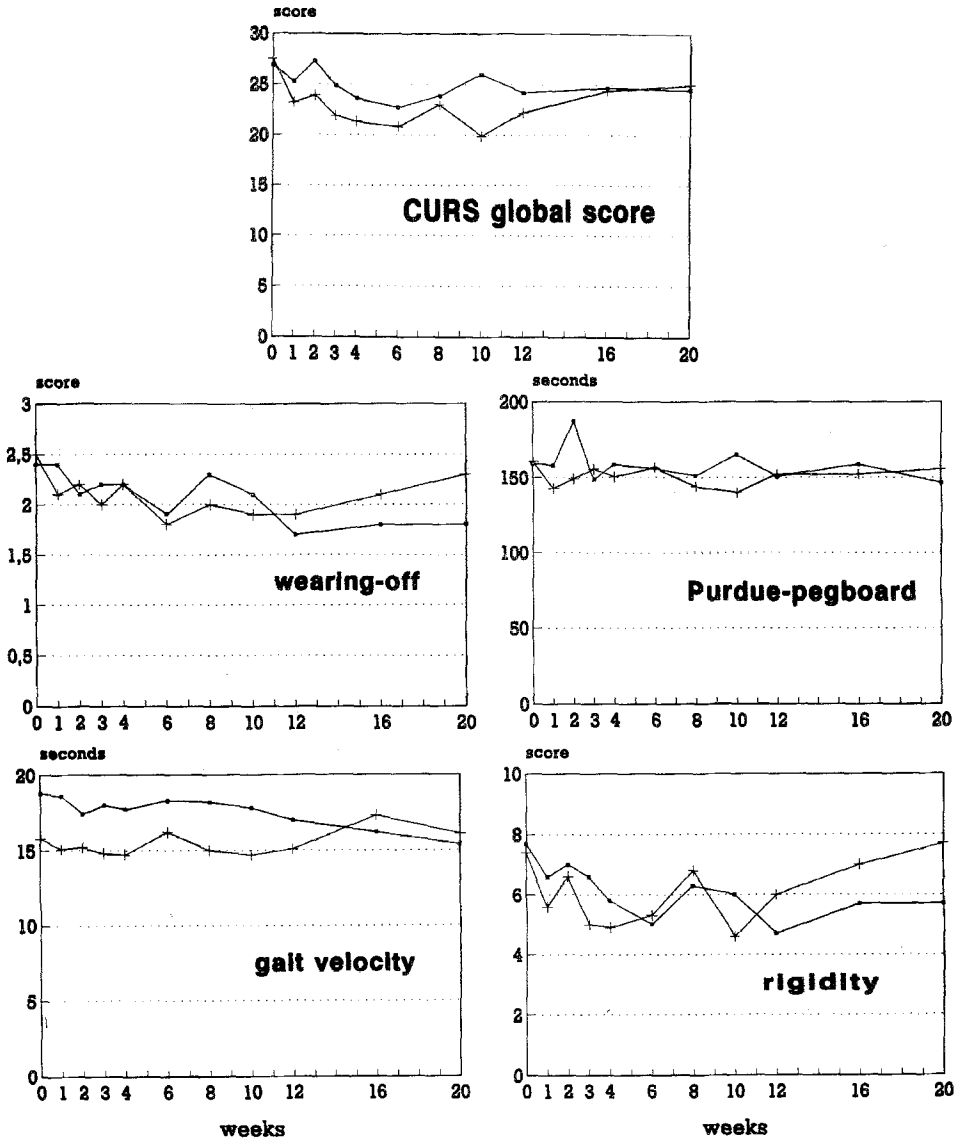

Fig. 1. The Columbia University Rating Scale (CURS) global score and some additional scores/subscores (wearing-off, gait velocity, Purdue-pegboard and rigidity) are presented. The mean scores for the Lamotrigine group are characterized by a square whereas the placebo group carries a cross (range of the SD in the LTG and the placebo group: CURS global score, ±6.3–±11.1 and ±4.5–±7.6; wearing-off, ±0.4–±1.1 and ±0.5–±1.3; gait velocity, ±2.5–±6.1; Purdue-pegboard, ±26–±55 and ±21–±65; rigidity, ±1.2–±3.6 and ±2.4–±4.0). The differences between the groups were not significant

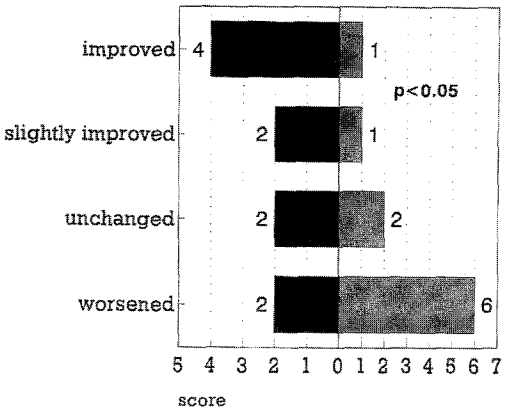

Fig. 2. The overall assessment of the clinical efficacy by the blinded rater is shown. The individuals of the Lamotrigine group are presented as black bars and of the control group as gray bars. The difference between the groups was significant ($p < 0.05$)

velocity, Purdue-pegboard and rigidity (Fig. 1)] showed a slight improvement in the LTG-group.

The overall assessment of the clinical efficacy by the blinded rater at the end point examination revealed marked differences between the two groups (Fig. 2). Significantly more patients under LTG-treatment than under placebo were classified as presenting an overall improvement. In addition in one patient receiving LTG a L-dopa dose reduction of 300mg/day was achieved.

Discussion

This double-blinded clinical study was conducted to confirm the results of our preceding open investigation on the therapeutic value of LTG for symptomatic treatment in PD (Zipp et al., 1993). It has to be pointed out that our study did not focus on any neuroprotective effects of LTG (McGeer and Zhu, 1990).

The use of LTG for the symptomatic treatment of PD is based on observations made in animal experiments which showed that anti-glutamatergic activities alleviate akinesia and muscular rigidity. Thus LTG might have antiparkinsonian effects or at least potentiate the therapeutic activity of levodopa (Greenamyre, 1993). At present clinical data are sparse, amantadine and memantine are the only NMDA-antagonists applicable in man (Kornhuber et al., 1991), but they have only a weak overall clinical efficacy.

Up to now most investigations have focussed on blocking postsynaptic receptor functions, especially NMDA-receptors. Our study tested a glutamate release blocker in PD modulating the glutamatergic activity presynaptically. In animal models it has been demonstrated that the overactive STN receives a glutamatergic input from the cortex which is not NMDA-mediated (Kitai and Kita, 1987; Rouzaire-Dubois and Scarnati, 1987a,b). Furthermore, it was recently shown in MPTP-treated mice that LTG influences the dopamine-depletion (Jones-Humble et al., 1994).

The results of our trial indicate that LTG is well tolerated by parkinsonian patients. A statistically significant difference between the two treatment-arms was seen with regard to the overall assessment. However, we were not able to confirm clearly our former data from a small open study which suggested a marked beneficial clinical effect of LTG in PD.

The number of patients in this controlled trial might have been too small to detect slight to moderate beneficial effects. This was stressed by the 6 drop-outs in which withdrawal was only partially referred to a worsening of the motor condition or to non-motor side effects. Therefore feasibilities for statistical evaluations were limited.

It should be taken into account that the duration of the trial was restricted to 6 months and that there might be a considerable number of non-responders as it has been observed in NMDA-antagonists such as the amantadine (Schwab et al., 1969).

LTG does not seem to have strong symptomatic antiparkinsonian effects. Nevertheless further trials are justified since the drug is well tolerated, and it remains to be clarified whether or not this compound mediates a slight general beneficial effect in PD; for such a study larger numbers of individuals are required.

Note added in proof

No beneficial effects were seen in the rat Parkinson model when LTG was injected i.p. [Löschmann P-A (1995) Eur J Pharmacol (in press)].

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Authors' address: Dr. H. Baas, PD, Department of Neurology, University of Frankfurt/Main, Schleusenweg 2-16, D-60528 Frankfurt/M., Federal Republic of Germany.

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