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Photosensitive epilepsy: a model to study the effects of antiepileptic drugs. Evaluation of the piracetam analogue, levetiracetam

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Abstract

The experimental antiepileptic drug, levetiracetam (UCB L059), a piracetam analogue has been investigated in photosensitive patients in the “photosensitivity model”, an early phase II study. A total of 12 patients (10 females, 2 males) with a mean age of 21.5 years (range 13–38) were investigated during a 3 day period in 3 centres (France, The Netherlands, Germany), using the same standardised method. The subjects were either treated with a single oral dose of 250 mg, 500 mg, 750 mg or 1000 mg. In addition, 4 patients took 250 mg b.i.d. for 3–5 days, after which they were re-examined. In 9 of 12 photosensitive patients (75%) a clear suppression (3 patients) or abolishment (6 patients) of IPS evoked photoparoxysmal EEG responses was found. This effect appeared to be dose-dependent, the higher the dose the greater the effect; complete abolishment was only seen at dosages of 750 mg and 1000 mg, occurring at peak plasma levels and lasting between 6 and 30 h. There was no indication of pharmacokinetic interaction with concomitant antiepileptic drugs such as valproic acid, ethosuximide or phenobarbitone. No serious side-effects were seen and some patients reported enhancement of their mood. Two patients with myoclonic jerks noticed a clear reduction of their myoclonus, although this was not one of the objectives of the study. In conclusion, levetiracetam showed a clear antiepileptic effect in the photosensitivity model.

Keywords: Levetiracetam; Photosensitivity; Trial model; Antiepileptic drugs

1. Introduction

Photosensitivity, defined as a generalized epileptiform reaction on intermittent photic stimulation (IPS)

outlasting the stimulus train is found in about 5% of epileptic patients [7].

Unlike most other epilepsies, photosensitive epilepsy is a reflex epilepsy and epileptiform discharges can be evoked at any time by intermittent photic stimulation (IPS) in the laboratory. By determination of both upper and lower sensitivity limits (frequencies per flash) a so-called photosensitivity

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range can be determined. This range is related to liability of seizures in daily life. A patient with a greater range has a higher likelihood of visual-induced seizures than those with a smaller range [7]. Furthermore, the photosensitivity range is relatively stable within a patient and can be diminished or abolished by antiepileptic medication, while no effect has been found when taking methohexitone and quinalbarbitone, the sleep-inducing non-antiepileptic barbiturates [3].

Besides the classical AEDs, the following drugs also diminished or abolished photosensitivity in at least 50% of the patients, e.g. progabide [1], lamotrigine [2], taltrimide, a taurine derivative [9], vigabatrin and loreclezole [11]. The experimental drug Org 6370 [8], however, has demonstrated paradoxical enhancement of photosensitivity with provocation of myoclonic seizures.

The technique of using the photosensitivity range proved therefore to be a good model to study the antiepileptic properties of a single dose of an experimental drug in humans in early phase II studies (so-called photosensitivity model) [3]. Furthermore, it is possible to explore the time, onset and duration of the effect, a dose-response relationship and to document plasma concentration-time profiles of the drug. Finally, certain data with regard to tolerability could be compiled in a drug not yet used in epileptic patients.

We present the results of assessing the effects of single oral doses of the potential new antiepileptic drug, levetiracetam, on the photosensitivity range in 12 photosensitive patients in a multicentre, multinational collaborative study.

Levetiracetam (UCB L059) is the *S*-enantiomer of α -ethyl-2-oxo-1-pyrrolidine acetamide, a piracetam analog [14]. Piracetam has been reported not only to lessen cognitive disturbances but also to reduce myoclonic jerks [4,5]. However, in order to be effective in the treatment of myoclonic jerks a very high dose of piracetam (up to 16 g/day or more) is necessary. Levetiracetam proved to show a potent anticonvulsant effect on relatively low doses (5–30 mg/kg) in various models of generalized seizures in rats and mice [6]. It also proved to be effective in the pentylenetetrazol (PTZ) and bicuculline-induced seizures but ineffective in the standard version of the maximum electroshock and subcutaneous PTZ seizures

tests [10]. Thus, results in animal models indicate that levetiracetam has a broad spectrum of anticonvulsant activity with a high therapeutic index.

The pharmacokinetics of levetiracetam show a rapid and almost completely absorption after oral administration. Peak plasma levels were generally reached within 1 h of administration. Urinary excretion of the unchanged compound represented approximately 50% of the dose administered. The half-life of the compound is in the range of 7–8 h for young healthy volunteers and 10–11 h for healthy elderly volunteers (older than 65 years).

Clinical studies with levetiracetam have been conducted to evaluate the effects of the compound in cognitive impairment and anxiety, especially in elderly patients [15]. Human volunteers and patients have reported adverse events, most often drowsiness, tiredness, general feeling of weakness and dizziness [15].

2. Materials and methods

2.1. Subjects

A total of 12 patients (10 females, 2 males) with proven photosensitive epilepsy and a mean age of 21.5 years (13–38) were investigated after informed consent was obtained. An equal number of patients were studied in France (Strasbourg, Marescaux), The Netherlands (Heemstede, Kasteleijn-Nolst Trenité) and Germany (Munich, Stodieck). All subjects were suffering from epilepsy (idiopathic, symptomatic or cryptogenic) with absence seizures (5), myoclonic jerks (4), tonic clonic seizures (2) and complex partial seizures (1) since the age of 3–23 (mean 9 years). Four patients were without co-medication; all other patients were on a stable regimen of valproic acid (200–2500 mg), ethosuximide (500 mg) or phenobarbitone (100 mg). The study protocol was approved by the 3 local ethical committees (CCPPRB, Strasbourg; Medical Ethical Review Board of the State University of Leiden; Ethisches Komitee Klinikum Grosshadern, Munich).

2.2. Procedure

The experimental procedure lasted 3 consecutive days in patients 1–8, and 5–7 days in patients 9–12.

Last mentioned patients were investigated after an acute single dose of 1000 mg levetiracetam and again after 3–5 days of subchronic oral treatment with levetiracetam 500 mg/day. These patients were re-examined with repeated IPS measurements after placebo at 8.00 h and a single dose of levetiracetam 500 mg at 10.00 h.

On the first day (baseline), quantitative assessment of the photosensitivity range was made by IPS during EEG investigations from 9.00 to 16.30 h, at 9.00, 10.00, 11.00, 13.00, 15.00 and 16.30 h, following a standardized procedure. If patients took concomitant antiepileptic medication, blood samples were drawn via an indwelling catheter, immediately following each IPS session.

On the second day (test day), the baseline photosensitivity range and blood level AED were re-established. A single oral dose of the experimental

drug was given at 9.00 h, after which serial estimations of IPS sensitivity ranges were performed at the same time schedule as on the first day, as were the blood samples.

On the third day, the procedure of the first day was repeated to investigate the duration of the observed facts. After the final session at 16.30 h routine neurological and laboratory safety examinations were performed.

Different single dosages of levetiracetam, i.e., 250 mg, 500 mg, 750 mg or 1000 mg were given for safety reasons and also to determine a possible dose-response relationship (Strasbourg 250 mg, Heemstede 500, 750 and 1000 mg, Munich 1000 mg). The experimental drug was administered orally in 250 mg capsules. Since the outcome parameter is abolishment or diminishment of the response to IPS (an electrophysiological response), not influenced by

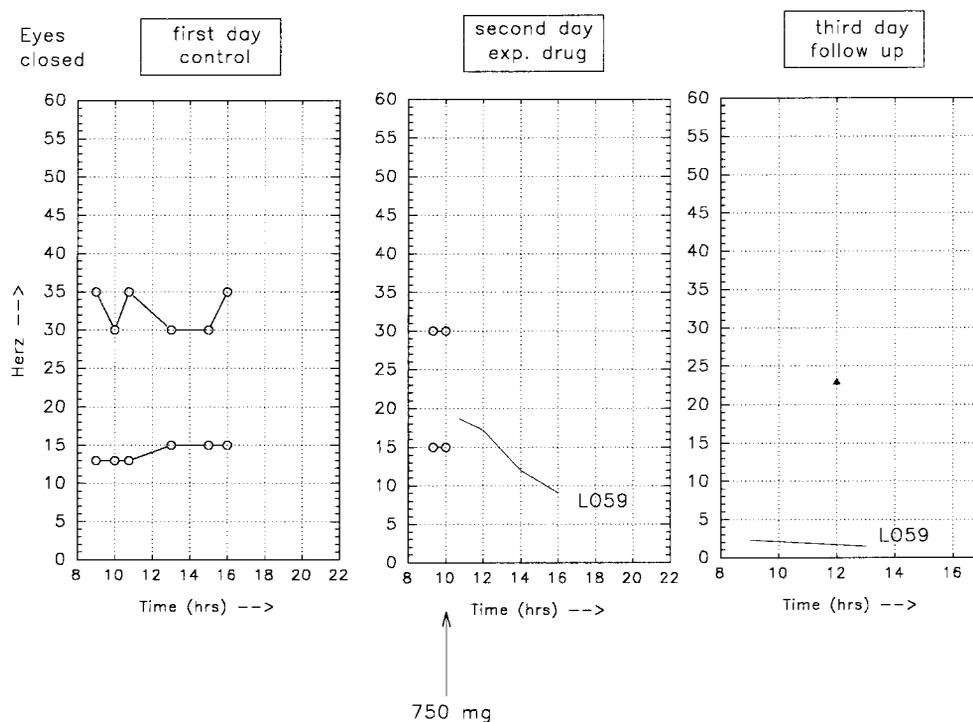


Fig. 1. The effect of oral intake of 750 mg levetiracetam (ucb LO59) on the photosensitivity range (upper minus lower limit, in Hz) in patient no. 8 is shown. The limits are graphically expressed as small circles. An abolishment of the reaction to intermittent photic stimulation (IPS) is seen 1 h after intake of the experimental drug on day 2. On the 3rd day at 12 h an epileptogenic reaction to IPS has returned, although not yet complete (▲) and only at one frequency (23 Hz). A correlation can be seen between the serum levels of LO59 and the suppressive effect of the drug.

“placebo” substances like sleep-inducing, non-epileptic substances [3], no placebo control was used. However, in order to avoid bias in assessment of the EEG data the final assessment was performed blinded.

The IPS procedure was standardized and carried out precisely the same at the 3 centres, using the photic stimulator (Grass PS22). Each IPS session was recorded with standard 21-channel EEG equipment and the records of the sessions were coded. Final blind assessment of all photosensitive ranges was carried out in Heemstede, The Netherlands. Only a response to IPS of generalized (ir)regular poly-spikes and waves, outlasting the stimulus train, was considered as positive; both an upper and lower limit (range) of photosensitivity could thus be estab-

lished per patient per IPS measurement (see for example Fig. 1).

2.3. Statistical analysis

Although the results are given descriptively, statistical analysis was also performed by comparing the areas per patient between upper and lower limits of the photosensitivity ranges on day 2 compared to day 1. A clear diminishment or abolishment of the photosensitivity range after intake of the single oral dose was considered as antiepileptic effect.

3. Results

All 12 epileptic patients completed the study; 9 of them showed a clear response to the experimental

Table 1
Results

Patients	Baseline IPS range (Hz)	Levetiracetam acute (mg)	Effect on photo- sensitivity range	Onset (h)	Duration (h)	Peak plasma level levetir- acetam (mg/l)	Side-effects start/stop * (min)
1	6–40 eye closure	250	diminishment 8 Hz	0.5–1	30	9.7	–
2	8–40 eye closure	250	only minor change 15–40	–	–	5.4	–
3	15–40 eye closure	250	only minor change 15–30	–	–	5.9	–
4	15–40 eye closure	250	no change	–	–	6.5	–
5	13–18 23–25 eye closure	500 1000	no change diminishment 22–25	– 0.5–1	– > 8	10.9 24.4	– dizziness 30/150
6	10–35 eyes closed	500	diminishment 20–25	0.5–1	6	11.2	–
7	15–25 eye closure	750	abolishment	0.5–1	24	16.6	–
8	15–35 eyes closed	750	abolishment	0.5–1	30	18.7	dizziness and nausea 30/210
9	8–45 eye closure	1000	abolishment	0.5–2	> 6	29.0	slight dysarthria, dysmetria, euphoric mood 90/210
10	15–60 eye closure	1000	abolishment	0.5–2	> 6	N.D.	–
11	6–60 eye closure	1000	abolishment	0.5–2	> 6	N.D.	–
12	6–60 eyes closed	1000	abolishment	1–2	> 6	N.D.	nausea, headache, euphoric 30/300

* Time after intake of levetiracetam.

N.D.: not done.

drug in terms of reduction/abolition of the photosensitivity (see Table 1). There was a significant relation between dose and effect (exact logistic regression analyses, $P = 0.01$, likelihood ratio test). The likelihood of effect was minimal at 250 mg and maximal at 1000 mg.

The maximum suppressing effect of EEG response to photostimulation in patients 1–9 occurred at the peak plasma level of levetiracetam (in the other 3 patients no blood levels were determined (protocol violation)). This effect was observed 1 h after intake of L059, except in patient no. 6 which was after 2 h. Remarkably, the 3 patients who took the lowest dosage (250 mg) and who did not react sufficiently to the drug showed a peak level only after 2 and even 4 h. Furthermore, only a suppressive reaction on the photosensitivity range was seen if the peak level of levetiracetam was at least about 10 $\mu\text{g}/\text{ml}$. The maximum peak level of levetiracetam appeared to be 29 $\mu\text{g}/\text{ml}$, in a patient with the highest dose per kg (16.1 mg/kg). In patients who had only a single intake of levetiracetam the duration of suppression of photosensitivity lasted between 6 and 30 h, while the plasma levels at that time were lower than 3 $\mu\text{g}/\text{ml}$. Eight out of 9 patients were treated with other AEDs (steady-state, VPA, ESM, PHB), of whom six took monotherapy VPA. No clear pharmacokinetic interaction was found between levetiracetam and the other antiepileptic drugs VPA, ESM or PHB; neither was there a sign of a pharmacodynamic interaction.

Side-effects of dizziness, nausea with dysarthria and ataxia were reported in 5 of the 12 patients at dosages of 750 or 1000 mg levetiracetam, starting at approximately peak plasma levels with a total duration of 0.5–5 h. Two patients felt more active and were euphoric.

Four patients (patients 9–12) continued treatment after the second day of investigation with 250 mg L059 b.i.d. These patients were subsequently investigated with serial photosensitivity measurements before and after intake of 500 mg levetiracetam. In three of the patients during subchronic dosages with 500 mg b.i.d. (patients 9–11), at trough levels of levetiracetam prior to drug intake on day 3, the photosensitivity range was greater than at 24.00 h after acute intake of 1000 mg. However, again abolishment of the response could be obtained after the

subsequent acute intake of 500 mg levetiracetam. In patient no. 12 complete abolishment was obtained after acute intake of 1000 mg levetiracetam and this effect was maintained during the steady-state period with 500 mg levetiracetam daily.

4. Discussion

In 9 of the 12 photosensitive patients (75%) a clear suppression or abolishment of IPS evoked photoparoxysmal EEG response was found after intake of a single oral dose of levetiracetam. This effect appeared to be dose-related with a maximum effect at 750–1000 mg (6 out of 7 patients). There was no indication for pharmacokinetic interaction with concomitant antiepileptic drugs such as valproic acid, ethosuximide or phenobarbitone. The maximum suppressing effect in these patients occurred at peak plasma levels of levetiracetam (especially if 10 $\mu\text{g}/\text{ml}$ or more), 1 h after intake of the drug except in one patient which was after 2 h. The duration of the suppressing effect lasted between 6 and 30 h, although the plasma levels of levetiracetam at that time were lower than 3 $\mu\text{g}/\text{ml}$. The relatively long duration of action, without a clear relationship to plasma levels, seems to be an important feature of this drug. The same but even a more pronounced effect has been found in acute studies with valproic acid [12,13]. They discovered that valproic acid started suppression of photosensitivity 3 h after peak plasma levels; this effect lasted for as long as 5 days, even without detectable levels of valproic acid in plasma. Whether or not metabolites could have been active in valproate is unknown. The major metabolite of levetiracetam is centrally inactive.

No serious side-effects were seen and some patients reported enhancement of their mood (see Table 1). Two patients with myoclonic jerks noticed a clear reduction of their myoclonus, although this was not one of the objectives of the study. One patient (no. 8) had a history of daily photic-induced myoclonic jerks with sufficient reduction of seizures with VPA medication but side-effects such as nausea and vomiting. She reacted to levetiracetam 750 mg in the trial and entered the open extension study on monotherapy levetiracetam. Using the IPS response as an effect parameter she was titrated up to 1000 mg levetiracetam. She continued taking the drug until

now (3 years 500 mg b.i.d.); no-side effects were registered and her myoclonic jerks remained fully controlled. Repeated IPS measurements confirmed this long-lasting suppressive effect of levetiracetam. Being a piracetam analog with a higher potency than piracetam, it is not surprising that levetiracetam has a special effect on myoclonic seizures. It seems therefore worthwhile to investigate the effect of levetiracetam, especially in epileptic patients with treatment-resistant myoclonic jerks such as progressive myoclonic epilepsy patients.

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References

- [1] Binnie, C.D., Pestre, M., De Korte, R.A., Kasteleijn-Nolst Trenité, D.G.A., Loiseau, P. and Meijer, J.W.A., Acute effects of single dose administration of progabide on human photosensitivity. In: G. Bartholini, L. Bossi and P. Morselli (Eds.), *LERS Monographs 3: Epilepsy and GABA Receptor Antagonists*, Raven Press, New York, 1985, pp. 311–319.
- [2] Binnie, C.D., Van Emde Boas, W., Kasteleijn-Nolst Trenité, D.G.A., De Korte, R.A., Meijer, J.W.A., Meinardi, H., Miller, A.A., Overweg, J., Peck, A.W. and Van Wieringen, A., Acute effects of lamotrigine (BW430C) in persons with epilepsy. *Epilepsia*, 27 (1986) 248–254.
- [3] Binnie, C.D., Kasteleijn-Nolst Trenité, D.G.A. and De Korte, R.A., Photosensitivity as a model for acute antiepileptic drug studies. *Electroenceph. Clin. Neurophysiol.*, 63 (1986) 35–41.
- [4] Brown, P., Steiger, M.J., Thompson, P.D., Rothwell, J.C., Day, B.L., Salama, M., Waegemans, T. and Marsden, C.D., Effectiveness of piracetam in cortical myoclonus. *Mov. Dis.*, 8 (1993) 63–68.
- [5] Chaudhry, H.R., Najam, N., De Mahieu, C., Raza, A. and Ahmad, B., Clinical use of piracetam in epileptic patients. *Epilepsia*, 32 (1991) 100.
- [6] Gower, A.J., Noyer, M., Verloes, R., Gobert, J. and Wülfert, E., Levetiracetam, a novel anticonvulsant drug: pharmacological profile in animals. *Eur. J. Pharmacol.*, 222 (1992) 193.
- [7] Kasteleijn-Nolst Trenité, D.G.A., Photosensitivity in epilepsy. Electrophysiological and clinical correlates. *Acta Neurol. Scand.*, 80 (1989) 1–149.
- [8] Kasteleijn-Nolst Trenité, D.G.A., Van Emde Boas, W., Groenhoet, C.M. and Meinardi, H., Preliminary assessment of the efficacy of Org 6370 in photosensitive epileptic patients: paradoxical enhancement of photosensitivity and provocation of myoclonic seizures. *Epilepsia*, 33 (1992) 135–141.
- [9] Keränen, T., Partanen, V.S.J., Koivisto, K., Tokola, O., Neuvonen, P.J. and Riekkinen, P.J., Effects of taltramine, an experimental taurine derivative, on photoconvulsive response in epileptic patients. *Epilepsia*, 28 (1987) 133–137.
- [10] Löscher, W. and Hönack, D., Profile of UCB L059, a novel anticonvulsant drug, in models of partial and generalized epilepsy in mice and rats. *Eur. J. Pharmacol.*, 232 (1993) 147–158.
- [11] Overweg, J. and De Beukelaar, F., Single-dose efficacy evaluation of loreclezole in patients with photosensitive epilepsy. *Epilepsy Res.*, 6 (1990) 227–233.
- [12] Rimmer, E.M., Milligan, N.M. and Richens, A., A comparison of the acute effect of single doses of vigabatrin and sodium valproate on photosensitivity in epileptic patients. *Epilepsy Res.*, 1 (1987) 339–346.
- [13] Rowan, A.J., Binnie, C.D., Warfield, C.A., Meinardi, H. and Meijer, J.W.A., The delayed effect of sodium valproate on the photoconvulsive response in man. *Epilepsia*, 20 (1979) 61–68.
- [14] Vermeij, T.A.C. and Edelbroek, P.M., High performance liquid chromatographic determination of levetiracetam (UCB L059) in human serum after solid-phase extraction. *J. Chrom. B: Biomed. Appl.*, (1994) 134–139.
- [15] UCB S.A. Pharma Sector, Investigator's Brochure RXCE93F2303 (August 30, 1993).