

EFFECTS OF NICERGOLINE ON THE RETINAL AND CORTICAL ELECTROPHYSIOLOGICAL RESPONSES IN GLAUCOMA PATIENTS: A PRELIMINARY OPEN STUDY

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Accepted 12 March 1999

Purpose: The retinal dysfunction and the delayed visual cortex responses shown by patients affected by glaucoma can be objectively assessed by Pattern Electroretinogram (PERG) and Visual Evoked Potentials (VEP) recordings. The present study aims to evaluate the effects of nicergoline on the retinal function and on the visual cortical responses in glaucoma patients. **Methods:** Sixty patients (mean age 44.6 ± 3.7) with open angle glaucoma were enrolled. The patients were divided into two groups: NG Group, where 30 patients were treated with nicergoline (Cebran[®], 2 cps day) for 30 days; and CG Group, where 30 patients were not treated. Simultaneous recordings of PERG and VEP were performed in NG patients at the baseline, at 30 days after treatment with nicergoline (day 30), and at 45 days from the end of the treatment (day 75). PERG and VEP were recorded in CG patients at the baseline and after 30 and 75 days. The visual stimulus for recording PERGs and VEPs was a checkerboard whose elements subtended a visual arc of 60' and 15' with a 70% contrast, and alternated at a frequency of 2 Hz. **Results:** At the baseline none of the electrophysiological parameters observed in NG Group patients differed ($P > 0.05$) from those of CG Group patients. At days 30 and 75, in CG Group patients the values of the PERG and VEP parameters were unmodified ($P > 0.05$) with respect to the baseline. In NG Group patients, the 30-day treatment period with nicergoline induced a significant ($P < 0.01$) improvement of the PERG and VEP parameters. At day 75 all the electrophysiological parameters of NG Group did not differ significantly ($P > 0.05$) from those at the baseline. **Conclusion:** Treatment with nicergoline induces an improvement of the retinal function and of the visual cortical responses in patients affected by glaucoma. This effect disappears within 45 days after the suspension of the treatment. © 1999 Academic Press

KEY WORDS: Glaucoma, nicergoline, visual evoked potentials, pattern electroretinogram, innermost retinal layer, visual pathways, visual function.

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INTRODUCTION

The clinical definition of glaucoma is based on the detection of an elevated intraocular pressure (> 21 mmHg) along with alterations of the optic nerve head and reduction of the visual field.

That glaucoma adversely affects visual function is common knowledge. The effects of glaucoma may be evaluated through subjective semeiological methods, such as the analysis of the visual field [1], of colour vision [2] and of contrast sensitivity [3]. However, as these methods are based on cortical psychophysical responses, they cannot provide specific information on the functionality of the various structures that determine a proper visual function (different retinal layers, optic nerve, post-chiasmatic visual pathways, visual cortex).

An objective evaluation of the single structures of the visual system may be obtained by recording the electroretinographic signals, evoked by flash (Flash ERG) or pattern (Pattern ERG—PERG) stimuli, and the bioelectric potentials of the occipital cortex, evoked by patterned stimuli (Visual Evoked Potentials—VEPs). Simultaneous recordings of PERGs and VEPs allow us to derive an electrophysiological index for the evaluation of the neural conduction in the post-retinal visual pathway: the retinocortical time (RCT) [4].

Recent studies report normal flash ERG [5, 6] and pathological alteration of PERG [5–15] and VEP [9, 11, 16–19] both in patients with glaucoma or ocular hypertension, and in animals with experimentally-induced glaucoma. Furthermore, a delay in RCT has been observed in glaucoma patients only [11, 19].

These electrophysical studies support the notion that glaucoma not only induces a dysfunction of the inner retinal layers [20], but also an impairment of the central nervous system (CNS) structures that contribute to the visual function [19]. These data are confirmed by the results obtained in brain autopsies of subjects affected by glaucoma [21], and by experimental studies on animals [22].

An important goal in glaucoma therapy is not merely to provide an adequate tonometric compensation, but also to improve the visual system function.

Insofar as glaucoma ultimately leads to alterations of some structures of the central nervous system it is reasonable to explore the therapeutic potential of drugs—such as citicoline—that are efficacious in vascular or cerebral degenerative conditions [23]. Indeed glaucoma patients treated with citicoline exhibit an improvement in the perimetrical indexes [24], as well as in the evoked retinal responses (PERG), cortical responses (VEP) and in the post-retinal neural conduction [25].

Another molecule that could improve the visual function in glaucomatous patients is nicergoline

(1.6 dimethyl-8b-(Bromoisonicotinoyloxmethyl)-10a-methoxyergoline).

Nicergoline is a molecule that has been used now for some time in cases of degenerative pathologies of the CNS where the lack of stimulating aminoacids may trigger a process of programmed cellular death with a consequent loss of neurons. Additionally, nicergoline displays antioxidant activity in cat brain homogenates, and as such could contribute to reducing the level of free radicals, thus lowering one of the most potent apoptotic signals. Furthermore, pharmacological and biochemical research *in vivo* has shown that nicergoline is one of the most potent inhibitors of the alpha-adrenergic receptors and specifically interacts with the D2 dopaminergic presynaptic receptors increasing the turnover of dopamine [26–33].

On this basis we undertook a study to evaluate the effect of nicergoline on the retinal cell function and on the post-retinal neural conduction in patients affected by glaucoma.

MATERIALS AND METHODS

Sixty volunteer patients with open-angle glaucoma were enrolled for the study. When the diagnosis of glaucoma was made, all patients had IOP > 21 mmHg (range 23–27, mean 24.10 ± 1.75 mmHg). Each patient received topical treatment with beta-blocker only and the IOP was < 21 mmHg (mean 17.8 ± 1.5 mmHg) in all patients enrolled; filtration surgery had never been performed. Other inclusion criteria were: glaucomatous optic nerve head cupping (cup/disc ratio > 0.5), glaucomatous visual field defects (Humphrey 24–2 perimetry with Mean Deviation between -2 and -4 dB), best corrected visual acuity of 20/20 or better; mean refractive error, when present, between -0.50 and $+0.50$ spherical equivalent. The mean age was 45.6 ± 4.3 years. The following exclusion criteria were adopted: presence of any general or ocular pathology that might have interfered with the study; verified intolerance to any ingredient of the drug to be tested; pregnant or nursing women.

CLINICAL PROTOCOL

The patients were divided into two age-matched groups:

- Thirty patients were treated for 30 days with 2 cps a day of nicergoline (Cebran[®], SIFI, Catania, Italia) (NG Group, 30 eyes);
- 30 patients that were not treated (CG Group, glaucomatous control patients, 30 eyes).

No other general pharmacological treatments were performed on all glaucoma patients during the whole

period of treatment with nicergoline, while the topical treatment with beta-blockers was continued. No differences in the IOP measurements were found between CG and NG patients (CG: 17.6 ± 1.4 mmHg; NG: 17.1 ± 1.6 mmHg).

Informed consent was obtained from each patient enrolled in this study and the research followed the tenets of the Declaration of Helsinki.

To evaluate the efficacy of the drug the retinal function and the neural conduction in the visual pathway was examined by an electrophysiological assessment.

Electrophysiological assessment

In NG patients simultaneous recordings of VEP and PERG were assessed in the basal condition (day 0), after a 30-day treatment period with nicergoline (day 30) and after a 45-day period of wash-out (day 75). In CG patients simultaneous recordings of VEP and PERG were assessed in the basal condition (day 0), and after 30 and 75 days.

The electrophysiological examinations were performed using a previously published method [19]. The subjects under examination were seated in a semi-dark, acoustically isolated room in front of the display that was surrounded by a uniform field of luminance of 5 cd m^{-2} . The subjects were informed of the type of examination and its diagnostic uses.

Prior to the experiment, each subject was adapted to the ambient room light for 10 min and the pupil diameter was approximately 5 mm.

The visual stimuli were checkerboard patterns [contrast expressed as $(L_{\text{max}} - L_{\text{min}})/(L_{\text{max}} + L_{\text{min}})$ was 95%, mean luminance 100 cd m^{-2}] generated on a TV monitor and reversed in contrast at the rate of 2 reversals s^{-1} . At the viewing distance of 114 cm the check edges subtended $60'$ and $15'$ of visual angle and the screen of the monitor subtended 12.5° . The refraction of all subjects was corrected for the viewing distance. The stimulation was monocular, after occlusion of the other eye.

VEP recordings Ag/AgCl cup shaped electrodes were fixed with collodion in the following positions: active electrode in Oz, reference electrode in Fpz, ground on left arm.

The interelectrode resistance was kept below 3 k Ω . The bioelectric signal was amplified (gain 20,000), filtered (band-pass 1–100 Hz) and averaged (200 events free from artifacts were averaged for every trial) by BM 6000 (Biomedica Mangoni, Pisa, Italy). The analysis time was 250 ms.

The transient VEP was distinguished by several waves with three peaks, which in normal subjects and in our experimental condition, appeared after 75, 100 and 145 ms. These peaks had negative (N75), positive (P100) and negative (N145) polarity, respectively.

PERG recordings The bioelectrical signal was recorded by means of Ag/AgG small cup shaped ■ electrodes placed on the inferior eyelid. Monocular electroretinograms were derived bipolarly between the tested (active electrode) and the patched (reference electrode) eye; the ground electrode was on Fpz. The interelectrode resistance was maintained lower than 3 k Ω . The signal was amplified (gain 50,000), filtered (band pass 1–30 Hz) and averaged with automatic rejection of artifacts (200 events free from artifacts were averaged for every trial) by BM 6000. The analysis time was 250 ms.

The transient PERG was distinguished by several waves with three peaks, that which in normal subjects and in our experimental condition, appeared after 35, 50 and 95 ms. These peaks had negative (N35), positive (P50) and negative (N95) polarity, respectively.

In the recording session simultaneous VEPs and PERGs were recorded at least twice and the resulting waveforms were superimposed to check the repeatability of the results.

VEP and PERG signals with signals-to-noise ratio > 2 were accepted. The noise was measured by recording the bioelectrical signals while the monitor was screened by a cardboard and a noise $< 0.1 \mu\text{V}$ (mean $0.085 \mu\text{V}$) was observed in all subjects tested.

For all VEPs and PERGs the peak latency and the peak amplitude of each of the waves were measured directly on the displayed records by means of a pair of cursors. Simultaneous recordings of VEPs and PERGs made it possible to derive the retinocortical time (RCT) as the difference between the VEP P100 and the PERG P50 peak latencies [4, 25].

Statistics The differences between NG and CG patients and the differences observed in each group with respect to the basal condition and to the examination previously performed, were evaluated by one-way analysis of variance for repeated measures (ANOVA) and a $P < 0.01$ was considered significant.

RESULTS

The mean data and statistical results are shown in Table I and in Figs 1 and 2.

In the basal condition, similar values of VEP and PERG parameters ($P > 0.05$) were observed in NG and CG patients. In CG patients, after 30 and 75 days, no significant changes ($P > 0.05$) of VEP and PERG parameters were observed, with respect to the values observed in the basal condition.

VEP recordings

NG patients: after 30 days of treatment (day 30), a significant ($P < 0.01$) decrease in P100 peak latencies and a significant ($P < 0.01$) increase in

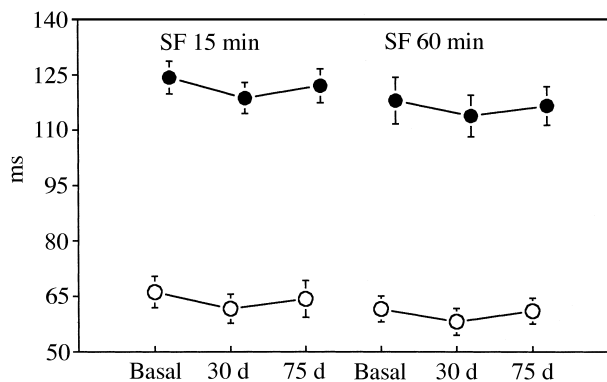


Fig. 1. Graphic representation of mean values of VEP P100 peak latency (●) and PERG P50 peak latency (○) observed in glaucoma patients treated with beta-blockers in basal condition and after medical treatment with nicergoline and beta-blockers. The treatment with nicergoline was performed over a 30-day period (30 d) followed by 45 days of wash out (75 d). Vertical lines represent 1 SD of the mean. SF: spatial frequencies used. The statistical analysis is reported in Table I.

N75–P100 peak amplitudes, with respect to the basal values, were found. At day 75, NG patients presented an increase in P100 peak latencies and a decrease in N75–P100 peak amplitudes, with respect to the values observed at day 30. No differences ($P > 0.01$) were found between VEP parameters with respect to the basal ones.

PERG recordings

NG patients: after 30 days of nicergoline treatment (day 30), a significant ($P < 0.01$) decrease in P50 peak latencies and a significant ($P < 0.01$) increase in P50–N95 peak amplitudes, with respect to the basal values, were found. After a period of 45 days of wash-out (day 75), an increase in P50 peak latencies and a decrease in P50–N95 peak ampli-

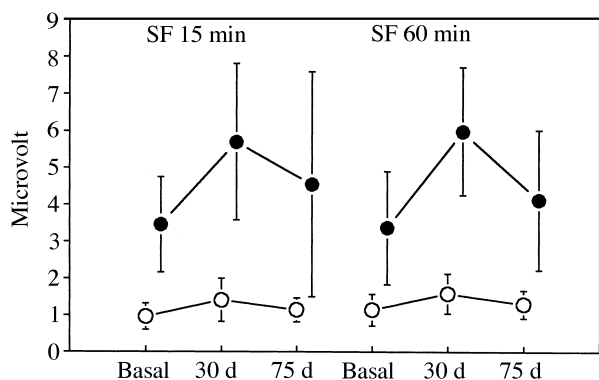


Fig. 2. Graphic representation of mean values of VEP N75–P100 peak amplitude and PERG P50–N95 peak amplitude observed in glaucoma patients treated with beta-blockers in basal condition and after medical treatment with nicergoline and beta-blockers. Vertical lines represent 1 SD of the mean. SF: spatial frequencies used. The statistical analysis is reported in Table I.

tudes, with respect to the values observed at 30 days, were observed and the PERG parameters were similar to the basal ones ($P > 0.05$).

Retinocortical time

NG patients: at day 30, a decrease of RCT, with respect to the basal values, was found ($P < 0.01$). At day 75, we observed an increase of RCT, with respect to the values observed at day 30, and its values were not significantly modified with respect to basal ones ($P > 0.05$).

During the whole period of treatment, no adverse side effects were reported from any of the patients enrolled in the study. No significant changes of the intraocular pressure were found in any of the subjects tested.

DISCUSSION AND CONCLUSION

The aim of the present study was to evaluate the effects of nicergoline on the functional responses of the retina and of the visual cortex in glaucoma patients.

We observed an improvement of the electrophysiological responses of the visual cortex (VEP), with a concomitant improvement of the retinal function (PERG) and of the post-retinal neural conduction (RCT) after the treatment with nicergoline.

The efficacy of nicergoline in the treatment of diabetic and hypertensive retinal ischaemic pathologies is recognised [34–36], and the results of the present study indicate that nicergoline has a positive effect on the function of the retina and the visual cortex, but the exact mechanism of action of this molecule on the visual system, is not well known. Treatment with nicergoline improved the VEPs of glaucoma patients. Thus, the electrophysiological data which indicate that nicergoline improves the cortical responses confirms what has been previously suggested by the psychophysical analysis [37].

As the variation of the VEPs observed in glaucoma patients has been ascribed to a dysfunction of the innermost retinal layers (ganglion cells and their fibers) correlated to a delay in the post-retinal neural conduction [11, 19], in the present study we have evaluated the effect of nicergoline on retinal function and on the neural conduction along the visual pathways.

Retinal function was evaluated by PERG recordings and our results indicate that nicergoline induces an improvement of retinal bioelectric activity (PERG with reduced latency and increased amplitude). However, as no morphological evaluation was conducted, nothing can be said about ulterior effects on the retinal nerve fibers (i.e. an increased thickness of retinal nerve layers fibers).

The observed PERG improvement could be at-

Table I

Mean values and 1 SD (\pm) of electrophysiological parameters observed in patients with glaucoma (GN Group) before (basal), after 30 days of treatment with nicergoline (30 days) and after 45 days from the end of the treatment (75 days). 15' and 60' spatial frequencies used. Statistics: one-way analysis of variance for repeated measures (ANOVA)

15' Parameters	Basal	30 days	75 days
VEP P100 latency (ms)	124.27 \pm 4.43	118.73 \pm 4.25 vs basal: $F_{1,59} = 24.43$, $P < 0.001$	122.13 \pm 4.62 vs basal: $F_{1,59} = 3.35$, $P = 0.072$ vs 30 days: $F_{1,59} = 8.80$, $P = 0.004$
VEP N75-P100 amplitude (μ V)	3.46 \pm 1.29	5.70 \pm 2.12 vs basal: $F_{1,59} = 24.44$, $P < 0.001$	4.55 \pm 3.05 vs basal: $F_{1,59} = 3.25$, $P = 0.077$ vs 30 days: $F_{1,59} = 2.88$, $P = 0.095$
PERG P50 latency (ms)	66.20 \pm 4.22	61.70 \pm 3.95 vs basal: $F_{1,59} = 18.18$, $P < 0.001$	64.33 \pm 4.96 vs basal: $F_{1,59} = 2.47$, $P = 0.121$ vs 30 days: $F_{1,59} = 5.16$, $P = 0.027$
PERG P50-N95 amplitude (μ V)	0.96 \pm 0.36	1.41 \pm 0.59 vs basal: $F_{1,59} = 12.72$, $P < 0.001$	1.14 \pm 0.33 vs basal: $F_{1,59} = 4.08$, $P = 0.048$ vs 30 days: $F_{1,59} = 4.79$, $P = 0.033$
Retino cortical time (VEP 100 — PERG P50 latencies, ms)	58.06 \pm 1.33	57.03 \pm 1.32 vs basal: $F_{1,59} = 9.06$, $P = 0.004$	57.80 \pm 2.33 vs basal: $F_{1,59} = 0.28$, $P = 0.598$ vs 30 days: $F_{1,59} = 2.48$, $P = 0.121$
60' Parameters			
VEP P100 latency (ms)	118.10 \pm 6.39	113.90 \pm 5.68 vs basal: $F_{1,59} = 7.24$, $P = 0.009$	116.67 \pm 5.27 vs basal: $F_{1,59} = 0.89$, $P = 0.348$ vs 30 days: $F_{1,59} = 3.83$, $P = 0.055$
VEP N75-P100 amplitude (μ V)	3.37 \pm 1.54	5.99 \pm 1.73 vs basal: $F_{1,59} = 38.39$, $P < 0.001$	4.13 \pm 1.90 vs basal: $F_{1,59} = 2.90$, $P = 0.094$ vs 30 days: $F_{1,59} = 15.72$, $P < 0.001$
PERG P50 latency (ms)	61.90 \pm 3.48	58.17 \pm 3.59 vs basal: $F_{1,59} = 16.70$, $P < 0.001$	61.60 \pm 3.45 vs basal: $F_{1,59} = 0.11$, $P = 0.742$ vs 30 days: $F_{1,59} = 14.24$, $P < 0.001$
PERG P50-N95 amplitude (μ V)	1.14 \pm 0.43	1.59 \pm 0.54 vs basal: $F_{1,59} = 12.75$, $P < 0.001$	1.30 \pm 0.38 vs basal: $F_{1,59} = 2.33$, $P = 0.132$ vs 30 days: $F_{1,59} = 5.79$, $P = 0.019$
Retino cortical time (Vep 100-PERG P50 latencies, ms)	56.50 \pm 1.64	55.30 \pm 1.66 vs basal: $F_{1,59} = 7.93$, $P = 0.007$	55.60 \pm 2.05 vs basal: $F_{1,59} = 3.53$, $P = 0.065$ vs 30 days: $F_{1,59} = 0.39$, $P = 0.536$

tributed to the activity on the metabolic rate, to the dopaminergic-like action of nicergoline, or to both.

Recent studies report that treatment with nicergoline during a concomitant treatment with beta-blockers may induce an improvement of the metabolic parameters of the retina in rats. In fact Drago *et al.* [38] observed that treatment with beta-blockers alone reduces the level of glucose, pyruvate, citrate and ATP, while the concomitant administration of nicergoline determines a normalization of these biochemical parameters. These results suggest that nicergoline may potentiate cellular metabolic rate and therefore prevent the biochemical alterations correlated to the use of beta-blockers.

Considering that all our patients were treated topically with beta-blockers alone, it could be suggested that nicergoline acts on the retinal cells with a similar mechanism. In fact, if the treatment with

nicergoline improves the metabolic rate of the retinal cells in glaucoma patients, it can also determine an improvement of the function of the retinal cells themselves.

Another valuable hypothesis that helps explain the improvement of the PERG is related to nicergoline's effectiveness in facilitating dopaminergic and cholinergic neurotransmission. Considering that levodopa induces an improvement of the retinal function which may be evaluated by PERG recordings [39], we may hypothesize that a similar neuromodulator activity could be considered at the base of nicergoline's ability to improve PERG in glaucoma patients.

Both mechanisms of action could help explain the significant increase in amplitude and decrease in latency of the PERG observed after the treatment with nicergoline.

Along with the retinal function the post-retinal neural conduction was evaluated by measuring the Retinocortical Time.

We observed a reduction of the RCT after the treatment with nicergoline in our glaucoma patients. This reduction may be ascribed to an improvement of the retinal function with a consequent improvement of the neural conduction along the visual pathways. This could induce an increase in the bioelectric activity of those cells in which the cortical potential originates with consequent reduced VEP P100 latencies and increased VEP N75–P100 amplitudes after the treatment with nicergoline. It would be of interest to corroborate the independent action of nicergoline on the post-retinal neural conduction and on the visual cortex, for which at present there is no direct evidence in the literature.

Therefore, the effects of nicergoline on the bioelectric responses of the visual cortex may be determined by two sources of improvement: one prevalent at the retinal level (PERG with reduced latency and increased amplitude) and one at the post-retinal level (decreased RCT).

We have previously observed that the perimetrical indexes (Mean Deviation of Humphrey's perimetry) are significantly correlated to the parameters of the PERG and VEP and to the RCT [40]. Therefore, the sources of cortical improvement mentioned in this study could probably also be used to explain the improvement of the perimetrical condition observed after the treatment with nicergoline [37].

In this study we have evaluated the long-term effects of nicergoline. All electrophysiological parameters of the glaucoma patients treated with nicergoline, observed after 45 days from the end of the treatment, were similar to those observed before the beginning of the treatment. This suggests that the retinal and cortical bioelectrical responses improve after 30 days of treatment, while it is not possible to observe any improvement 45 days after the suspension of the treatment.

Concluding, nicergoline significantly improves the retinal and visual cortical bioelectric responses in glaucoma patients.

As the effects of nicergoline on normal human retinal and cortical responses are unknown at present and on account of nicergoline being effective in several other disorders [26–31], we believe that this drug cannot be considered a specific treatment in glaucoma. Nevertheless, our results suggest a potential use of this substance in the medical treatment of glaucoma as a complement of the hypotensive therapy and the absence of collateral effects offers an additional advantage.

Further work will be required to corroborate our conclusions and to determine the effect of various treatment schemes.

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