

Visual Acuities and Scotomas After One Week Levodopa Administration in Human Amblyopia

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The authors previously showed that a single dose of levodopa improves the contrast sensitivity and decreases the size of fixation point scotomas in amblyopic patients. In the present study, they investigated the effect of levodopa after 1 wk of daily administration using a cross-over, double masked design. The decrease of fixation point scotomas was confirmed with automatic static perimetry. An improvement of visual acuity occurred in 70% of the patients after 1 wk of levodopa administration compared to only 22% in the authors' previous study using one single dose. The improvements in visual acuities and visual fields persisted even after the levodopa administration was completed. Invest Ophthalmol Vis Sci 33:2722-2728, 1992

The neurotransmitter dopamine is present in retinal amacrine and interplexiform cells,¹ and it is likely involved in information processing to the brain.^{2,3} Investigations have shown the involvement of dopamine in various visual functions.⁴⁻⁹ Visual evoked responses,³ electroretinograms,¹⁰ and contrast sensitivity^{3,11} are changed in patients with Parkinson's disease. Levodopa administration also influences various electrophysiologic parameters in normal subjects.¹²⁻¹⁴

We showed, in a preliminary study that included nine adult amblyopic patients, that a single dose of orally administered levodopa had a positive short-term effect on their visual functions.¹⁵ Ninety minutes after administration of levodopa, we found an increase in the contrast sensitivity and a reduction in size of the fixation point scotoma. In that study, scotomas were measured by dynamic manual perimetry with the Aulhorn phase difference haploscope. Visual acuity improved a half-line in two out of the nine patients tested. Leguire and coworkers¹⁶ confirmed our results in amblyopic children 8-12 yr old. After a

single dose of levodopa, they found a slight increase in contrast sensitivity of the amblyopic eyes. The amplitude of pattern-visual evoked potential improved by 41%. The most impressive change was in visual acuity. Mean values of Snellen line acuity improved about 1.5 lines in their patients.

The aim of our study was to investigate the effect of an increased duration of levodopa administration in a larger group of patients. We were especially interested in whether continuous levodopa treatment for a week would further improve visual functions and increase the visual acuities in patients older than 12 yr. The manual dynamic perimeter (Aulhorn phase difference haploscope) used in our preliminary study was replaced by an automatic static perimeter for measurements of the binocular fixation point scotoma of the amblyopic eyes. The later technique allowed us to measure small relative scotomas, whereas only absolute scotomas can be measured with the Aulhorn phase difference haploscope.

Patients and Methods

Twenty patients with strabismic or anisometropic amblyopia were included in a cross-over, double masked, placebo-controlled study after the nature and possible consequences of the study were fully explained and after informed consent was obtained. The study was approved by the Institutional Review Board of the Wills Eye Hospital. Before the study began, all patients underwent an initial complete ophthalmologic examination, including perimetry of the fixation point scotoma to determine eligibility for participation and to familiarize them with the testing. Refractive errors were determined by retinoscopy and were fully corrected. Nineteen patients had no other

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ocular pathology than amblyopia. Patient 2 had strabismic amblyopia and infantile nystagmus. During the study, Snellen visual acuity and visual fields of the amblyopic and dominant eyes for each patient were measured five times at weekly intervals, always at the same time each day. The first visit marked the beginning of the study. The second visit occurred after 1 wk of oral administration three times a day of 2 mg/kg levodopa or placebo. The third visit followed a 1 wk interval without drugs. The fourth visit was after 1 wk oral administration opposite the earlier three times a day of 2 mg/kg levodopa or placebo. The fifth and final visit occurred after a 1 wk interval without any drugs.

After each 1 wk treatment of levodopa or placebo, patients were asked whether subjective changes or side effects had occurred. Patients were randomly divided into two groups of 10. Group I received levodopa during the first week of the study and placebo during the third week. Group II received the opposite, placebo during the first week and levodopa during the third week. The Pharmacy Department of Wills Eye Hospital prepared for each patient 21 levodopa capsules with 2 mg/kg body weight and 21 placebo capsules. No peripheral decarboxylase inhibitor was added to the levodopa. The placebo was made with the same capsules used for levodopa, but they were filled with lactose instead of the active drug. Neither patients nor examiners were aware of the difference. Patients were advised to take one capsule three times per day at approximately 8 hr intervals, with the last

capsule to be taken about 1 hr before the examination. In general, compliance of patients taking the medication was good. Two patients missed one pill during the levodopa treatment, while only one patient missed one pill during the placebo administration. All other patients took all 21 pills of placebo and levodopa. Clinical details of patients in group I and group II are summarized in Table 1.

The visual acuities of the patients' amblyopic and dominant eyes were measured sequentially at each examination. Snellen visual acuity was measured at all examinations with the same projector unit. One full line of Snellen letters was presented to the patients. Patients were asked to read each letter from left to right. When patients were unable to read all letters from a line correctly, the examination was stopped. If patients could read only some of the letters from a line, the denominator of the Snellen acuity was changed as a function of the percentage of correct letters. For example, a patient correctly reading the entire 20/70 line and two out of four letters of the 20/60 line would be classified as having a visual acuity of 20/65. For statistics, we used the logarithm of the decimal acuity to obtain an equal discriminability scale for the visual acuity.¹⁷

Fixation point scotomas of the amblyopic eyes were measured with automatic static perimetry using the vision monitor (Metrovision; Villeneuve, France) under binocular conditions. Patients were fully corrected and wearing additional spectacles with a green filter (Kodak [Rochester, NY] Wratten 58) in

Table 1. Clinical characteristics of patients

Patients	Age (yr)	Sex	Visual acuity		Class	Squint angle
			Right eye	Left eye		
Group 1						
1	26	male	20/200	20/20	anisometropic + strabismic	16 esotropia 4 right hypertropia
2	13	male	20/60 - 1	20/100	strabismic (infantile nystagmus)	12 exotropia
3	17	male	20/15	20/60 - 2	strabismic	20 esotropia
4	26	male	20/40 - 1	20/20	strabismic	20 esotropia
5	52	female	20/20	20/200	strabismic	10 esotropia
6	58	female	20/20	20/300	strabismic	20 esotropia
7	57	male	20/20	20/200	strabismic	10 esotropia
8	12	male	20/20	20/80 - 1	anisometropic	4 exotropia
9	30	male	20/200	20/20	anisometropic + strabismic	60 esotropia
10	26	male	20/20	20/40 - 1	anisometropic + strabismic	6 esotropia
Group 2						
11	16	male	20/20	20/60 - 1	anisometropic + strabismic	6 esotropia
12	56	female	20/70 + 3	20/20	strabismic	4 esotropia
13	54	male	20/20	20/200	strabismic	65 exotropia
14	29	male	20/20	20/60	anisometropic	2 exotropia
15	22	female	20/400	20/20	anisometropic + strabismic	10 esotropia
16	21	female	20/15	20/300	anisometropic	orthotropia
17	12	female	20/40	20/25	anisometropic	orthotropia
18	22	male	20/20	20/80 - 1	anisometropic + strabismic	15 exotropia
19	21	female	20/15	20/40 + 1	strabismic	18 esotropia
20	14	female	20/15	20/400	anisometropic + strabismic	10 esotropia

front of the amblyopic eye and a red filter (Kodak Wratten 25) in front of the dominant eye without correction of the strabismic angle. Test spots of 12.6 arc min were presented for 300 ms on a cupola with high mesopic white background illumination (1 cd/m^2) at 33 cm from the subject's eye. A green interferential filter (MTO [Massy, France] DH485b; peak of transmission of 80% at 485 nm, bandwidth 160 nm) was inserted in the stimulus projection beam and was seen only by the amblyopic eye. Test spots were projected at 40 different locations in the central 8° (16° diameter) of the cupola using a staircase procedure for threshold measurements (bracketing 4/2). A red light-emitting diode source (635 nm) located in the center of the cupola was seen only by the dominant eye and was used for fixation. Because the strabismic angle was not corrected, we did not measure the central scotoma, but measured the fixation point scotoma of the amblyopic eye. The latter corresponds to the fixation point or the fovea of the dominant eye. A white fusion pattern made of portions of arcs seen by both eyes was projected on the cupola between 8° and 12° from the center. Subsequently, the patient was asked to remove the color filter spectacles and the amblyopic eye was patched. Monocular static perimetry of the dominant eye was performed using the same test paradigm.

Threshold values were specified as the logarithm of the stimulus attenuation ($1 \text{ dB} = 0.1 \text{ log units}$). The reference of the logarithmic scale (0 dB) is the maximum luminance obtained with the green stimulus, the maximum obtained with a white stimulus being 318 cd/m^2 . Patient reliability was measured with false positive and false negative responses. They were found to be between 0% and 20% in all patients except patient 2 with infantile nystagmus that gave up to 50% false positive and 60% false negative responses.

Results

The mean visual acuity of the 10 patients of group I at each of the five examinations is represented in Figure 1A. Compared to the first examination, an increase of the mean visual acuity was obtained after 1 wk of levodopa administration at the time of the second examination. At examinations three to five, the mean visual acuity remained approximately unchanged. An analysis of variance for repeated measures was performed. A statistically significant ($P < 0.05$) improvement in visual acuity was found after the levodopa treatment between examinations one and two. After examination two, visual acuity remained improved throughout the study. Visual acuities were significantly better at examinations two, three, four, and five than at examination one. No significant change was observed after placebo administration between examinations three and four. Figure

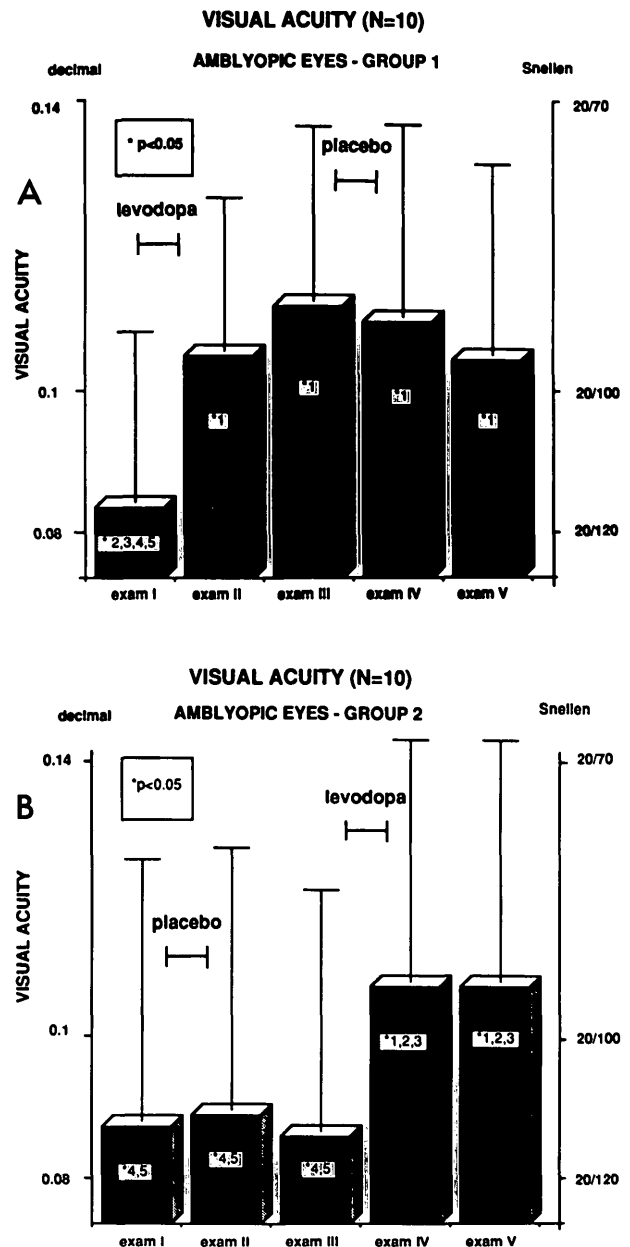


Fig. 1. Means \pm standard errors of visual acuities of patients in Group 1 (A) and patients in Group 2 (B) at each of the five examinations. Numbers shown in boxes on the columns correspond to examinations (1 = exam I, 2 = exam II, etc.). For each column, these numbers indicate significant differences between the corresponding columns and the other examinations listed. Bars indicate the 1 wk levodopa or placebo administration.

1B displays mean values of visual acuities from the patients of group II at each of the five examinations. No significant change was observed between examinations one, two, and three.

Placebo administration during the week between the first and second examination did not influence visual acuity. After levodopa administration, at the fourth examination, a statistically significant improvement in visual acuity was observed. At the fifth exami-

nation, after a 1 wk interval without drug administration, the visual acuity remained unchanged compared to examination four and was significantly better than at examinations one, two, and three. After levodopa administration, 14 patients measured an improvement in visual acuity, and in six patients, the visual acuity remained unchanged. In 10 patients, the increase in visual acuity was less than one line, and in four patients it was more than one line. The maximum improvement in one patient was one-and-a-half lines. A paired t-test indicated that the visual acuity of all 20 patients was significantly better ($P = 0.0013$) after levodopa administration than before levodopa administration. No statistically significant correlation was found between the change in visual acuity after levodopa administration and the age of the patients or the level of visual acuity found at the beginning of the study. After placebo administration, five patients measured an improvement in visual acuity, visual acuity decreased in four patients, and no change of visual acuity was measured in 11 patients. No significant difference between values of visual acuity before and after placebo administration was found with the paired t-test.

No significant changes in visual acuity were found in the dominant eyes after levodopa or placebo administration.

In two patients, one from each group, we were not able to complete the visual field measurements of the amblyopic eyes. Patient 13, with a large exotropia of 65 prism diopters, could not detect the test spot at the highest illumination level, and patient 2, with infantile nystagmus, admitted after the end of the study that he had closed the dominant eye during part of the examinations. A low reliability of his visual field examinations was reflected in a high percentage of false positive and false negative results. Visual fields of the amblyopic eyes of these two patients were excluded from further evaluation. All other patients showed good compliance and completed all examinations.

In Figure 2A, the mean values of visual field deficits of the amblyopic eyes of the nine remaining group I patients are represented at each examination time. After levodopa administration, at the second examination, the visual field deficit decreased significantly compared to the first examination ($P < 0.05$). Placebo administered between examinations three and four did not improve the mean visual field deficit of the patients. The mean values of visual field deficit of group II at each examination time are plotted in Figure 2B. No statistically significant changes were found between the different examinations.

Placebo administered between examinations one and two did not improve the visual fields deficit. Levodopa, given after the third examination, decreased the

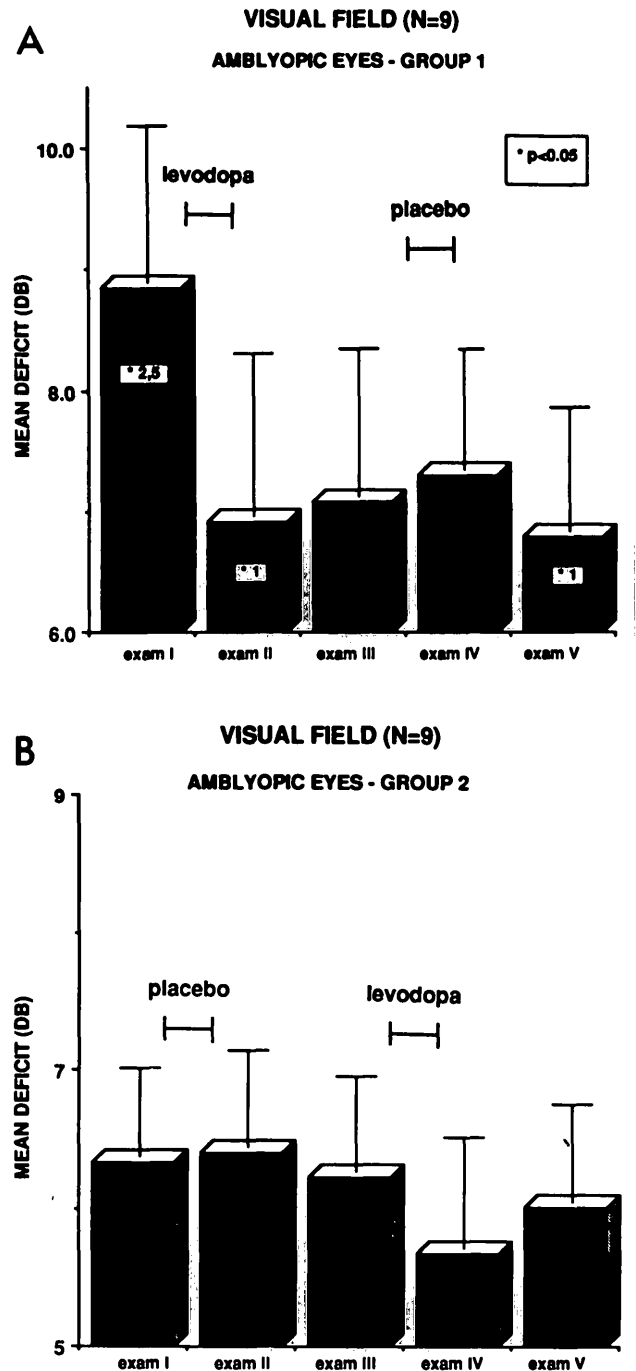


Fig. 2. Means \pm standard errors of visual fields of amblyopic eyes of patients in Group 1 (A) and patients in Group 2 (B) at each of the five examinations. Numbers shown in boxes on the columns correspond to examinations (1 = exam I, 2 = exam II, etc.). For each column, these numbers indicate significant differences between the corresponding columns and the other examinations listed. Bars indicate the 1 wk levodopa or placebo administration.

mean deficit slightly, but not significantly. After levodopa administration, the mean visual field defect decreased in 15 patients and increased in three patients. A statistically significant difference ($P = 0.009$) was found with the paired t-test. No statistically signifi-

cant correlation was found between the change of mean visual field deficit after levodopa administration and the patients' ages or the mean visual field deficit at the beginning of the study.

Ten patients were found to have an increase, seven patients had a decrease, and one patient showed no change of the mean deficit of the visual field before

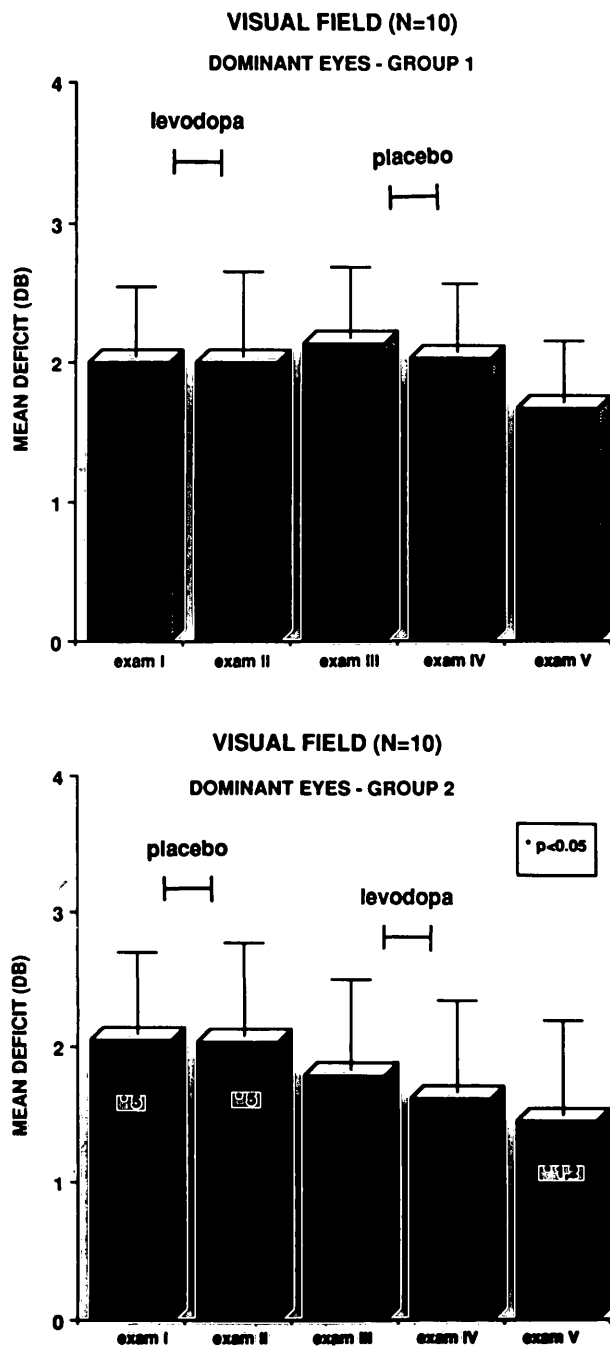


Fig. 3. Means \pm standard errors of visual fields of dominant eyes of patients in Group 1 (A) and patients in Group 2 (B) at each of the five examinations. Numbers shown in boxes on the columns correspond to examinations (1 = exam I, 2 = exam II, etc.). For each column, these numbers indicate significant differences between the corresponding columns and the other examinations listed. Bars indicate the 1 wk levodopa or placebo administration.

and after placebo administration. No significant difference was found after placebo administration.

In Figure 3A, mean values of visual field deficits of the dominant eyes of group I patients are displayed. No significant changes were observed between the different examination dates. No effect of levodopa or placebo was observed. Results from the mean values of visual field examinations from group II are represented in Figure 3B. No significant difference was observed after placebo administration between examinations one and two or after levodopa administration between examinations three and four. However, the mean visual field deficit decreased significantly at examination five compared to examination one and two.

Patients were asked, after each sequence of levodopa or placebo administration, whether they experienced any subjective visual changes and side effects. Four patients indicated, after levodopa treatment, that they could see better, objects were easier to discriminate, and light was brighter. None of the patients had subjective visual changes after placebo administration. Three patients had mild nausea or stomach cramps and one patient felt a little dizzy for a short time during the levodopa treatment. Three patients complained of mild headaches during the placebo administration. Because these symptoms were nonspecific and occurred after levodopa and after placebo, they did not unmask to which group the patients belonged.

Discussion

The present double-masked, placebo-controlled study confirms that levodopa influences at least two different visual functions in human amblyopia. We found improvements in visual acuities and decreases in the mean defects of the fixation point scotomas, reflecting the degree of binocular suppression. The improvements of visual acuities and visual fields were persistent 1–3 wk after the levodopa administration was completed.

A significant improvement in visual acuity after levodopa administration in both groups of patients and in all 20 patients grouped together was found. Visual acuity improved in 14 out of 20 patients (70%) after levodopa. In the present study, after 1 wk of levodopa treatment, the improvement of visual acuity occurred more frequently compared to our previous report, where only two out of nine patients (22%) had a mild improvement in visual acuity after a single dose of levodopa.¹⁵ This might be attributed to the longer levodopa administration in our present study or to differences between patients participating in each study. The age distribution among patients of the present study (12–58 yr) and those participating in our previous study (18–48 yr) as well as the visual acuity (20/

400 to 20/30 in the present study and below 20/100 in all patients included in the previous study) were not similar. However, patients over a wide range of age and visual acuities were included in the present study and we did not find a statistically significant correlation between the effect of levodopa on visual acuity, the age of patients, their visual acuity, or the size of suppression scotoma at the beginning of the study. Therefore, it is most likely that the more frequent improvement in visual acuity in the present study was caused by the longer administration period of levodopa. Although the improvement in visual acuity was small in most of the patients participating in the study, we found an improvement of visual acuity of more than one line in four patients. The maximum increase in visual acuity was one-and-a-half lines in one patient.

In contrast, Leguire and coworkers¹⁶ found an impressive mean 1.5 lines increase of the Snellen visual acuity in their four patients after a single administration of levodopa. The two main differences between Leguire et al's study and our study were that all of their patients were younger than 12 yr and that he used higher dosages of levodopa. It is possible that the visual system of patients under 12 yr of age is much more susceptible to levodopa than that of older patients. The higher dosage of levodopa used by Leguire and coworkers, between 100 and 400 mg, might also have contributed to the larger improvements of visual acuity they obtained. However, most of their patients had pronounced side effects, such as vomiting or nausea.

We used a new technique for measuring the fixation point scotoma. Static automatic perimetry with separation of both eyes with red/green glasses and with a white fusion stimulus presented to both eyes was employed. This technique had all of the advantages that static automatic perimetry has over a manual dynamic test. Threshold measurements at 40 different locations allowed us to measure small relative scotomas from patients with only mild suppression. With the phase difference haploscope, in contrast, only absolute scotomas can be measured. In addition, automated perimetry minimizes influences of the examiner on perimetry results. In two patients, we could not complete the visual field measurements as described in the text results. The inability of these two patients to complete the test would have been the same with the Aulhorn phase difference haploscope. In all other patients, cooperation and ease of use of the test were excellent. One possible disadvantage of the new method could be, however, a reduction of binocular suppression resulting from the color separation of the eyes' images.

The mean visual field deficit of all 18 patients showed a significant decrease after levodopa adminis-

tration. These results agree with our previous study, where the size of visual field defects decreased in all patients. Because of different methods of perimetry, it is difficult to compare precisely the results from the two studies. However, levodopa decreased scotomas in most of the amblyopic patients in the two studies.

The effect of levodopa on visual acuity and on visual fields did not decline immediately after the levodopa administration was stopped. Although levodopa administration was completed in the patients of Group I and Group II, visual acuity remained significantly improved until the end of the study (3 wk after the end of levodopa administration in Group I and 1 wk in Group II). In Group I, the decrease of the mean visual field defect also lasted until the end of the study, 4 wk after the levodopa administration was stopped. These results suggest that the improvement of visual functions persisted even after the drug was stopped. A learning effect resulting from improved compliance throughout the study could have caused a persistent improvement. However, Figure 1 clearly shows that no improvement in visual acuity or visual field was noticed after placebo and that improvements were always associated with levodopa administration. In patients who received the placebo first, no improvements were measured until they received the levodopa. Improvements of visual acuities and visual fields did not occur gradually over time. This argues against a learning effect causing the long-term improvement of visual functions. In the dominant eyes, levodopa or placebo administration did not have a significant effect. This supports the specificity of the effect of levodopa on the amblyopic eyes. In Group II, significant improvements of visual fields were observed at examination five compared to examinations one and two. Here the improvement of the visual field occurred gradually after the second examination. This effect appears to be more likely a result of learning. No gradual visual field improvement occurred in the amblyopic eyes.

Only four patients with anisometric amblyopia without strabismus participated in this study. In these patients, improvement of visual fields and visual acuities were observed after levodopa administration. However, the number of anisometric patients was too small to be compared statistically to the strabismic patients.

Subjective improvement occurred in four patients after levodopa treatment, but in none of the patients after placebo. Patients said they could see better, discriminate objects easier, and that light was brighter. These changes were nonspecific, but could correspond to less suppression and better visual acuity after levodopa administration.

None of our patients experienced dramatic side effects. Although three patients had mild stomach

cramps and nausea during a short period of the levodopa administration, they could not decide whether the mild side effects were caused by the levodopa or by some nonspecific infection or a mild reaction to food.

So far, the mechanism of action of levodopa remains unclear. Because dopamine is present in the human retina¹ and also appears to be involved in visual information processing to the brain,^{2,3} the dopaminergic effect cannot be localized to a specific part of the visual pathway.

In conclusion, the present study confirms that levodopa favorably influences visual functions in amblyopia by increasing visual acuity and decreasing binocular suppression. The larger number of patients with improved visual acuity after 1 wk of levodopa administration compared to those who received a single dose suggests a dose-dependent response. This needs to be investigated further using higher doses with longer duration of administration. A persistent effect also is suggested in this study and warrants further investigations at longer time intervals from the drug administration. A larger number of patients is needed to show whether some patients are more responsive to levodopa than others.

Key words: dopamine, levodopa, human amblyopia, visual acuity, fixation point scotoma

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