

EFFECT OF VITAMIN A TREATMENT ON THE PROLONGATION OF DARK ADAPTATION IN STARGARDT'S DYSTROPHY

ANDREW M. GLENN, FRCS, FCOPTH, GERALD A. FISHMAN, MD,
LEONARDO D. GILBERT, COT, DEBORAH J. DERLACKI, BA

Background: Prolongation in recovery of rod thresholds has been demonstrated in Stargardt's dystrophy. One possible explanation for this finding includes an impairment of vitamin A transport by the retinal pigment epithelium (RPE). By delivering an increased amount of vitamin A to the RPE, it might be possible to overcome a relative deficiency of vitamin A utilization or transport, and thus improve rod dark adaptation.

Methods: Baseline dark-adapted rod final thresholds were measured for five patients with Stargardt's dystrophy after 60 minutes of dark adaptation. A full dark-adaptation curve was then measured after exposure to a bleaching light for 5 minutes. Time of recovery to within 0.2 log units of the prebleach dark-adapted rod threshold was determined. Each subject then took a 14- to 18-day course of oral vitamin A, 50,000 IU daily. Dark adaptation was then reassessed using the same pretreatment protocol.

Results: Before treatment, all five patients had a prolongation of their rod recovery curve. There was no statistically significant difference between subjects in mean time taken to reach prebleach rod baseline thresholds before and after vitamin A treatment.

Conclusions: These findings do not rule out the possibility that a delay in rod dark adaptation in Stargardt's dystrophy results from an inability to transport vitamin A from the RPE to photoreceptor cells. Nevertheless, a high dose of oral vitamin A taken for at least 14 days did not provide any objective improvement in dark-adaptation function in five such patients.

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Prolongation in the recovery of rod thresholds has been demonstrated in Stargardt's dystrophy.¹⁻³ Prolongation in dark adaptation has also been reported in

From the Department of Ophthalmology and Visual Sciences, UIC Eye Center, University of Illinois at Chicago, College of Medicine, Chicago.

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Reprint requests: Gerald A. Fishman, MD, UIC Eye Center, University of Illinois at Chicago, 1855 West Taylor Street, Chicago, IL 60612.

patients with retinitis pigmentosa,⁴⁻⁷ choroideremia,⁸⁻¹⁰ and in vitamin A deficiency.¹¹ The pathogenic mechanism responsible for prolonged dark adaptation in patients with Stargardt's dystrophy remains obscure; however, among several possibilities is a quantitative or qualitative defect in a carrier protein of vitamin A in the retinal pigment epithelium (RPE), or an impairment of vitamin A transport in the RPE because of the accumulation of a lipofuscin-like pigment within the RPE cells.

In vitamin A deficiency, depletion of ocular stores of vitamin A results initially in a prolongation in recovery of rod function and then elevated rod dark-adapted

thresholds.¹¹ Replenishment of vitamin A corrects this abnormality in dark adaptation. We speculated that in patients with Stargardt's dystrophy, by delivering an increased amount of vitamin A to the RPE, it might be possible to overcome a relative deficiency in vitamin A utilization or transport at the RPE cell level and thereby to improve rod dark adaptation.

In the current study, we assessed the effect of high-dose oral vitamin A therapy on the prolonged recovery of rod thresholds in five patients with Stargardt's dystrophy. Dark adaptation recovery curves were compared before and after a 2-week course of oral vitamin A therapy, 50,000 IU daily.

Patients and Methods

Patients

Five patients with Stargardt's dystrophy, three men and two women, were included in the study. Their ages ranged from 24 to 49 years (mean, 34.4 years). Three were black and two white. None had any systemic disease (such as diabetes) that might affect retinal function. Additionally, none had liver or gastrointestinal disease that might prevent or reduce absorption of oral vitamin A. Two subjects were taking a multivitamin preparation (containing vitamin A, 30 IU daily), which was stopped within 1 week of the trial. One subject continued taking vitamin C; otherwise, no subjects took any medication during the period when the high doses of vitamin A were being ingested.

None of the subjects had evidence of autosomal dominant inheritance. Funduscopically, all had atrophic-appearing lesions in the fovea. Two patients had flecks limited to within 1 disc diameter of the foveal margin and were classified as having Stage 1 disease according to Fishman's classification,¹² and three had more extensive flecks, classified as Stage 2.

On Goldmann visual field testing, three subjects had central scotomas to the V-4-e target and fixated eccentrically in a stable and reproducible location, which was assessed by fixation fundus photographs. Two additional subjects with central fixation had no central scotoma to the V-4-e target, although one had a relative central scotoma to the II-4-e target and the other to the II-2-e target only.

Methods

Each subject underwent a full ophthalmic examination, including best corrected visual acuity, slit-lamp and fundus examination, and Goldmann visual fields with V-4-e, II-4-e, and II-2-e test targets. Patients were asked if they subjectively noticed a delay in the rate of adjusting to darkness.

Dark adaptation was tested on a Goldmann-Weekers dark adaptometer by a method previously described,² using a flickering (0.5-Hz) 2° test target stimulus of either blue (transmission peak, approximately 460 nm) or orange (90% transmission at 590 nm) light. One eye of each subject was selected on the basis of the best acuity or the smallest central scotoma (left eye in three and right eye in two subjects).

After pupillary dilatation to 7 to 8 mm, the test eye was dark adapted for 60 minutes with the use of an occlusive patch, and the subject was placed in a dimly lit room.

A baseline dark-adapted rod final threshold was measured in four retinal locations in the vertical meridian between 10° and 40° from fixation, in the superior and inferior retina. A test site in the superior retina was selected outside any scotoma to the Goldmann perimeter II-2-e target, and rod thresholds were measured at 5° above and below this point to ensure that a similar threshold was present around the primary tested locus, so that a modest fixation movement during testing would not affect the interpretation of prebleach and postbleach thresholds. The test eye then was exposed to a bleaching light of 3.1 log cd/m² for 5 minutes (after 2 minutes in room light), which bleached approximately 67% of the rhodopsin.

A full dark-adaptation curve was measured at the selected test site. The orange and blue test stimuli were alternated so that a curve for each was obtained. The end point of rod adaptation was defined as a return to within 0.2 log unit of the prebleach dark-adapted rod threshold.

Subjects then took a 14- to 18-day course of high-dose oral vitamin A (Aquasol A, 50,000 IU daily; Astra, Westboro, MA). This dosage, which is 15 times the recommended dietary allowance,¹³ may increase the serum vitamin A level by approximately 10% to 16%.^{14,15} On the final day of treatment, dark adaptation was reassessed by the method already described under identical conditions and at the same time of day (all testing was performed in the morning). Dark-adaptation tests on all patients were performed by the same examiner.

Results

Data for the five subjects are shown in Table 1. Before treatment, all had a prolongation of the rod recovery curve, confirming previous findings.¹⁻³ A representative dark-adaptation curve (Patient 2) is shown in Figure 1; the curves for before and after vitamin A treatment are virtually identical. Figure 2 shows the dark-adaptation curve of a normal subject tested under identical conditions.

The mean difference between pretreatment and post-treatment values for the time to reach the prebleach rod threshold for the five patients was -1.2 minutes. An

approximate 95% confidence limit for the mean difference in the time to reach the prebleach rod threshold was -5.2 to $+2.8$ minutes, which indicates that there was no statistically significant difference in the mean time to reach the prebleach rod baseline threshold, before and after vitamin A treatment. A student's statistic was used to determine the above.

Patient 5 was given a second course of vitamin A, 6 weeks after the initial course, because he was unable to attend for dark-adapted testing after the first course. The results for Patient 5 show a more elevated prebleach baseline dark-adaptation rod threshold after vitamin A treatment than either before vitamin A use or at a subsequent baseline dark-adapted threshold obtained 60 days after the use of vitamin A. This may be due to a shift of criterion for responding to the stimulus, rather than a true elevated rod threshold related to vitamin A treatment, because after the 60-day washout period after the second course of vitamin A, the baseline rod threshold was found to be similar to the prebleach, pretreatment baseline rod threshold. Further, the actual dark-adaptation recovery curves for before and after vitamin A treatment were virtually identical.

All patients completed their full course of vitamin A treatment (50,000 IU). As indicated, none had any underlying disease likely to prevent adequate absorption or cause a preexisting vitamin A deficiency. Two subjects who reported a subjectively prolonged period for dark adaptation before treatment observed no improvement during or after oral vitamin A treatment. Two subjects noted normal rates of adjusting to dark both before and after treatment, and one subject reported a normal rate of adjusting to dark before treatment with a better than normal rate after treatment.

No change in fundus appearance was noted on clinical examination after treatment. One subject reported a severe headache of 12 hours' duration while receiving treatment; otherwise, no adverse effects were noted.

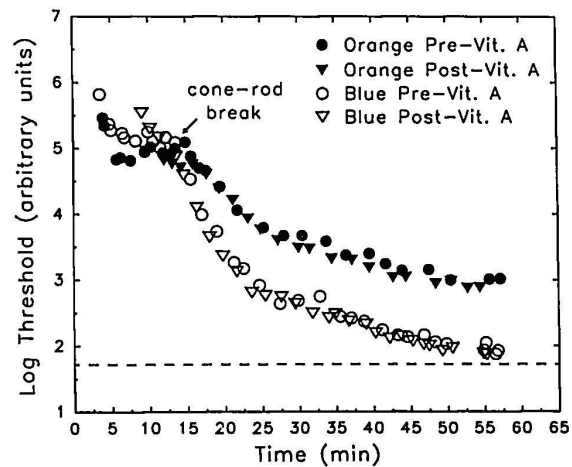


Fig. 1. Dark-adaptation curves for patient 2, before (Pre-Vit. A) and after (Post-Vit. A) treatment with vitamin A. The dashed line indicates prebleach, dark-adapted rod threshold.

Discussion

Stargardt's dystrophy is inherited as an autosomal recessive trait in most cases and is one of the most common juvenile macular dystrophies that can lead to legal blindness. Visual acuity can decrease rapidly to 20/200 once the acuity decreases to 20/40.¹⁶ Visual acuity tends to stabilize at the 20/200 to 20/400 level.

A prolongation of dark adaptation has been reported¹⁻³ in such patients, which can be demonstrated as a delay in the recovery of the later portion of the rod recovery curve. Although the cause of this observation is not apparent, we conjectured that a defect in the regeneration of rhodopsin, resulting from a quantitative or qualitative defect of a transport protein for vitamin A within RPE cells, or perhaps from an inability to transport vitamin A because of the accumulation of a lipofuscin-like substance within these cells, might account for the prolongation in rod recovery.

Table 1. Dark-Adaptation Findings Before and After Vitamin A Treatment in Patients With Stargardt's Dystrophy

Patient No.	Dark-Adapted Prebleach				Time to Reach Prebleach Threshold (min)	
	Rod Threshold* (log cd/m ²)		Rod-Cone Break (min)		Pre Rx	Post Rx
	Pre Rx	Post Rx	Pre Rx	Post Rx		
1	-5.1 (1.9)	-5.0 (1.9)	12.5	12.0	54.0	56.5
2	-5.2 (1.7)	-5.2 (1.7)	14.0	14.0	50.0	47.0
3	-5.3 (1.6)	-5.6 (1.4)	17.0	15.0	61.0	65.0
4	-4.9 (2.0)	-5.1 (1.8)	14.0	13.0	60.0	57.5
5	-5.5 (1.4)	-5.0 (1.9)	13.0	12.0	48.0	41.0
Normal values						
Mean	-5.1 (1.8)		9.6		31.4	
Range	-4.9 to -5.2 (1.7 to 2.0)		7.3 to 12.2		27 to 39	

* Values in parentheses are arbitrary log units.
Rx, Treatment with vitamin A.

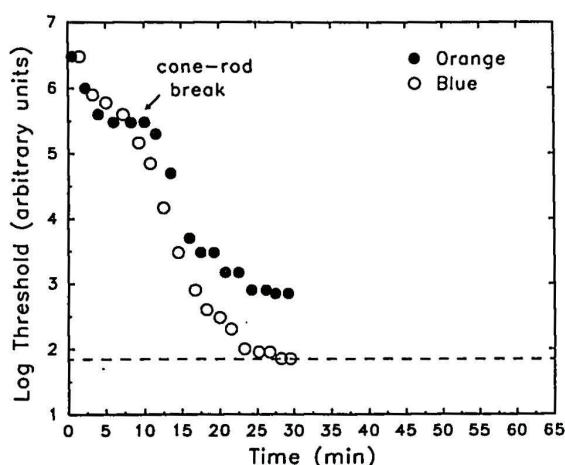


Fig. 2. Dark-adaptation curve for a normal subject. The dashed line indicates prebleach, dark-adapted rod threshold.

The explanation for the delay in dark adaptation in patients with Stargardt's dystrophy has yet to be determined. Our findings do not rule out the possibility that a delay in rod dark adaptation in these patients results from an inability to transport vitamin A from RPE to photoreceptor cells. Nevertheless, a high dose of oral vitamin A taken for a 14-day period did not provide any subjective or objective improvement in dark-adaptive function in five such patients.

Serum vitamin A concentration rises transiently after oral intake of vitamin A and returns to normal as the vitamin A is stored, mainly in the liver, in the form of retinyl esters. With excess dietary vitamin A intake, large amounts of retinyl ester are stored in the liver.¹⁷ Vitamin A is released from the liver, bound to retinol-binding protein (RBP), at a rate that is controlled by the serum levels of RBP-retinol complex, so that the serum retinol concentration is closely regulated. After long-term ingestion of excessive vitamin A, a constant elevation of the serum level occurs, presumably after storage sites have been filled, when vitamin A is transported in the serum as retinyl esters bound to lipoproteins in addition to RBP-bound retinol.¹⁸

Previous studies using nontoxic doses have suggested that a small increase (10% to 16%)^{14,15} in serum retinol levels can occur with high-dose oral vitamin A treatment after 3 to 6 months, presumably before saturation of liver storage. This may not represent a real increase, but rather a short-term variation. Because the RBP level was shown not to increase,¹⁴ any elevation of retinol level may be due to saturation of circulating RBP.

It may be possible to increase the serum vitamin A levels substantially for several hours, with each oral dose, although this increase would be mainly in the form

of retinyl esters in chylomicra¹⁷ and likely unavailable to the RPE. The elevation in serum retinol levels may be insufficient to impact favorably on rod dark adaptation, assuming that defective vitamin A transport was in fact responsible for the prolonged rod recovery.

Key words: dark adaptation, Stargardt's dystrophy, vitamin A.

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