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Effects of Multiple Doses of Voriconazole on the Vision of Healthy Volunteers: A Double-Blind, Placebo-Controlled Study

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Key Words

Voriconazole · Antifungal · Electroretinogram · Vision · Retina · Enhanced visual perceptions · Blurred vision · Photophobia

Abstract

Purpose: To investigate the effects, and their reversibility, of multiple oral voriconazole doses on a variety of visual tests in healthy male volunteers. ***Methods:*** Single-center, double-blind, randomized, placebo-controlled, parallel-group study in 36 volunteers who received voriconazole (n = 18, 400 mg every 12 h on day 1, then 300 mg every 12 h for 27.5 days) or matched placebo (n = 18). Electroretinograms (ERGs) and ophthalmological examinations were performed at screening, throughout the study and at follow-up. ***Results:*** Fifteen (83.3%) volunteers treated with voriconazole experienced ≥1 treatment-related visual adverse events (AEs); these included enhanced visual perceptions, blurred vision, color vision changes and photophobia. No serious AEs were reported. Voriconazole reduced from baseline scotopic maximal a- and b-wave amplitude, shortened implicit time and decreased oscillatory potential amplitude compared with placebo. Under photopic conditions, the 30-Hz flicker response amplitude was significantly reduced and was accompanied by a slight but nonsignificant prolongation of peak time. These effects did not progress in degree over the treatment period, and mean changes from baseline in ERG parameters were similar to placebo by day 43 (14 days after end of treatment). In the first week, color vision discrimination was impaired in the tritan axis, although this resolved by end of treatment and was similar to placebo by day 43. Mean deviation in the static visual field indicated increased sensitivity following voriconazole treatment, correlating with decreased amplitude in conjunction with shortened implicit time. ***Conclusions:*** Effects of voriconazole on altered visual perception, ERG, color vision and static visual field thresholds are nonprogressive over a treatment period and reversible. It is hypothesized that voriconazole has a pharmacological effect on rod and cone pathways including a possible mechanism of disinhibition that reversibly puts the retina in a more light-adapted state and leads to increased relative contrast sensitivity.

Introduction

Voriconazole is a broad-spectrum, triazole antifungal agent that is approved around the world for the treatment of systemic fungal infections, including those due to *Aspergillus* spp., *Candida* spp., *Scedosporium apiospermum*

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and *Fusarium* spp. Voriconazole is active against fluconazole- and itraconazole-resistant *Candida* and *Aspergillus* spp., has a favorable safety profile and is available in both oral and intravenous formulations [1, 2].

The most frequent adverse drug reactions with voriconazole are alterations in visual perception. This has been observed in 23–35% of patients in clinical trials [1, 3, 4], although in a large, prospective clinical trial in candidiasis, only 4% (11/300) of patients reported a visual adverse event (AE) [5]. The majority of reported events can be classified into 4 categories: enhanced/altered visual perception (i.e. objects appearing brighter); subjective symptoms of blurred vision; color vision change, and, photophobia manifesting as glare or dazzle. Enhanced/altered visual perception is the most frequently reported visual AE. These visual disturbances are usually transient (30–60 min duration) and fully reversible, diminish during repeated dosing and rarely (0.5%) require drug discontinuation [1, 3, 4].

This study further investigated the clinical observation that voriconazole-induced visual AEs are fully reversible. Electroretinograms (ERGs) can be sensitive measures of certain drug-induced alterations of retinal function [6, 7]. Change in ERG parameters was therefore selected as the primary end point. Secondary end points included the effects of voriconazole on color vision, visual fields and visual acuity.

Previous physiological studies had suggested that the site of voriconazole action on the visual system was most likely within the retina. For instance, reductions in the amplitude of the ERG (a-wave and b-wave) were noted in dogs, as well as humans [8]; the magnitude of the reductions was proportional to the plasma concentration, but there were no morphometric, morphological or histological changes in the eye or retina in 12-month toxicology studies in dogs to suggest that any irreversible damage or degeneration had occurred [8].

Another previous study investigated the effect of a single intravenous voriconazole (8 mg/kg) dose on the ERG, electro-oculogram, visual evoked potential and Farnsworth-Munsell 100 (FM-100) hue tests in 8 healthy males [8]. Voriconazole produced a statistically significant decrease in the electro-oculogram light rise (approx. 22%), mildly prolonged the P100 amplitude peak in the visual evoked potential and significantly reduced the ERG b-wave amplitude by 34% but not the a-wave. These reductions in b-wave amplitude were not evident at the follow-up visit. These previous results were used to refine the design of the visual safety study described here, which aimed to evaluate the reversibility of visual AEs of voriconazole following multiple dosing in healthy volunteers and investigate visual function before, during and after treatment.

Methods

Study Design

This was a single-center, double-blind, randomized, placebo-controlled, parallel-group study in healthy male volunteers. In one group, volunteers (n = 18) were treated with 400 mg voriconazole orally on day 1 (every 12 h), followed by 300 mg orally from day 2 to 28 (every 12 h), with a single-dose administration only on the morning of day 29. The second group (n = 18) received matched placebo on days 1–29. On visual assessment days, the study medication was administered in the clinic; on nonassessment days, the volunteers were instructed to take the medication at home.

This study was conducted in compliance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Rennes Institutional Review Board (Comité consultatif de protection des personnes dans la recherche biomédicale, Brest, France), and written informed consent was obtained.

Healthy male volunteers aged 18–45 years, weighing 60–100 kg, with a body mass index between 18 and 28 – weight (kg)/height^2 (m) – and with a normal electrocardiogram at screening were enrolled. Volunteers with poor metabolism status with respect to the CYP2C19 genotype or evidence of any clinically significant disease or abnormality were excluded. Volunteers with visual defects and ocular abnormalities that may have confounded assessment, including best-corrected visual acuity worse than 20/20, abnormal results for the baseline ERG or the other standard tests of visual function, were excluded.

The volunteers underwent a physical examination at screening, on days 1, 7, 14, 21, 28 and 42 (2 weeks after the last dose). Plasma samples were taken before dosing on days 1, 7, 14, 21 and 28 to determine trough concentrations of voriconazole and its primary metabolite, to verify that volunteers were taking the medication as instructed.

Primary End Point – ERG

An ERG was performed during screening and on days 1, 8, 29 and 43, 1 h after dosing with study treatment according to the International Society for Clinical Electrophysiology of Vision (ISCEV) international standard [9]. A Metrovision Cupola Stimulator (Metrovision, Pérenchies, France) was programmed according to the 5 steps of the ISCEV standard recordings [9]. The volunteers had each eye maximally dilated with 10% phenylephrine and 0.5% tropicamide. The volunteer was dark-adapted for at least 25 min. The ERG was recorded simultaneously from each eye using corneal contact lens electrodes (Metrovision). Both eyes were evaluated separately throughout the study; the average was determined for each volunteer where data were available for both eyes.

Dark-adapted retinal function was assessed via a 3-step series of stimulus flashes: step 1, a dim white light (0.001 cd s/m^2); step 2, a white ISCEV standard flash (close to 3 cd s/m^2); step 3, the electronic low-pass filter was increased to approximately 100 Hz, and a standard flash was administered with repetitions 15 s apart in order to record oscillatory potentials. The volunteer was subsequently light adapted for 10 min to a steady white background (close to 30 cd/m^2).

A photopic study was then performed in steps 4 and 5, applying an ISCEV standard flash for recording a photopic single flash cone response and a 30-Hz flicker response in order to assess cone function.

The primary variables were defined as the b-wave amplitudes at steps 1 and 2 in the dark-adapted state, oscillatory potential amplitude of the second wavelet (OP 2) at step 3 as well as step 4 (cone single flash response), and flicker response amplitude at step 5 from the ERG. Additionally implicit times for all these responses were evaluated and analyzed. The results were reviewed by a panel of independent experts who were asked to judge the quality of the data, the validity of the assessment, and the interpretation of the results.

Secondary End Points

The FM-100 hue test, automated visual field assessment (Humphrey Field Analyzer), visual acuity assessment by means of Early Treatment of Diabetic Retinopathy Study charts, dilated funduscopy and slitlamp, and external eye examinations were performed by an ophthalmologist during screening and on days 3, 7, 28 and 42. As the ability to perform the FM-100 hue and visual field tests can improve with experience, these tests were carried out on two separate occasions before treatment, and the result of the second test was used as the baseline score.

FM-100 Hue Test

The FM-100 hue test assesses the volunteer's ability to arrange 85 randomly shuffled colored disks in 4 trays in an order of minimally changing hues [10]. An error score was generated for each disk, based on how far the disk position was away from those disks that should have been adjacent to it in the correct order of hues; the summation of these individual error scores was the total error score. Due to time constraints, the test was only performed on a single eye (the same eye throughout the study) using standardized light conditions. Color discrimination ability and the type of color deficiency were visualized by a polar plot of the error scores.

Humphrey Visual Field Test

Visual fields were assessed using the Humphrey Field Analyzer Program 30-2 according to published methods [11]. Visual field data with fixation loss scores of 20% or more and false-positive or false-negative errors of 33% or more were considered unreliable and were excluded. Each visual field was graded as normal or abnormal and the character of any abnormality was noted. To facilitate the extended safety assessment of possible AEs and the possible relationship between phosphenes, blurred vision and cortical mechanism, visual fields were assessed and evaluated separately for both eyes.

Visual Acuity, Slitlamp, Retinal Morphology and External Eye Examination

Standard Early Treatment of Diabetic Retinopathy Study (ETDRS) charts were used to assess visual acuity at a distance of 4 m. Visual acuity was recorded in decimal values. Any abnormalities of the cornea, anterior chamber, iris lens or anterior vitreous during slitlamp testing or changes of appearance, reflexes or movements in external eye examination were recorded. Retinal morphology was examined in mydriasis using direct and indirect funduscopy.

Statistical Methods

Statistical analyses were performed on the ERG data from the evaluable population, which included all volunteers who completed the study to day 43, or who withdrew (due to visual disturbances) and had assessments prior to discharge and at follow-up. A sample size of 36 volunteers (18 per treatment group) was estimated to be sufficient to achieve statistical significance with a true difference of 20% or more in the amplitude of the ERG b-wave for photopic white light stimulus with >80% power when tested at the 5% level (two-sided). This calculation was based on data from a previous study where the between-volunteer standard deviation was estimated to be 17.55 μV [data on file, Pfizer Inc.].

ERG analyses were carried out on data from days 1, 8, 29 and 43, separately for each eye throughout the study; the average was determined for each volunteer where data were available for both eyes. On each day and for every parameter, the difference between treatment groups was estimated along with corresponding 95% confidence intervals. Comparisons were made using two-way analysis of covariance with treatment as a factor and screening data as a covariate; $p \leq 0.05$ indicated a significant treatment difference, but no adjustments for multiple comparisons (multiple end points and time points) were made, so p values should be interpreted more descriptively.

Results

Study Population

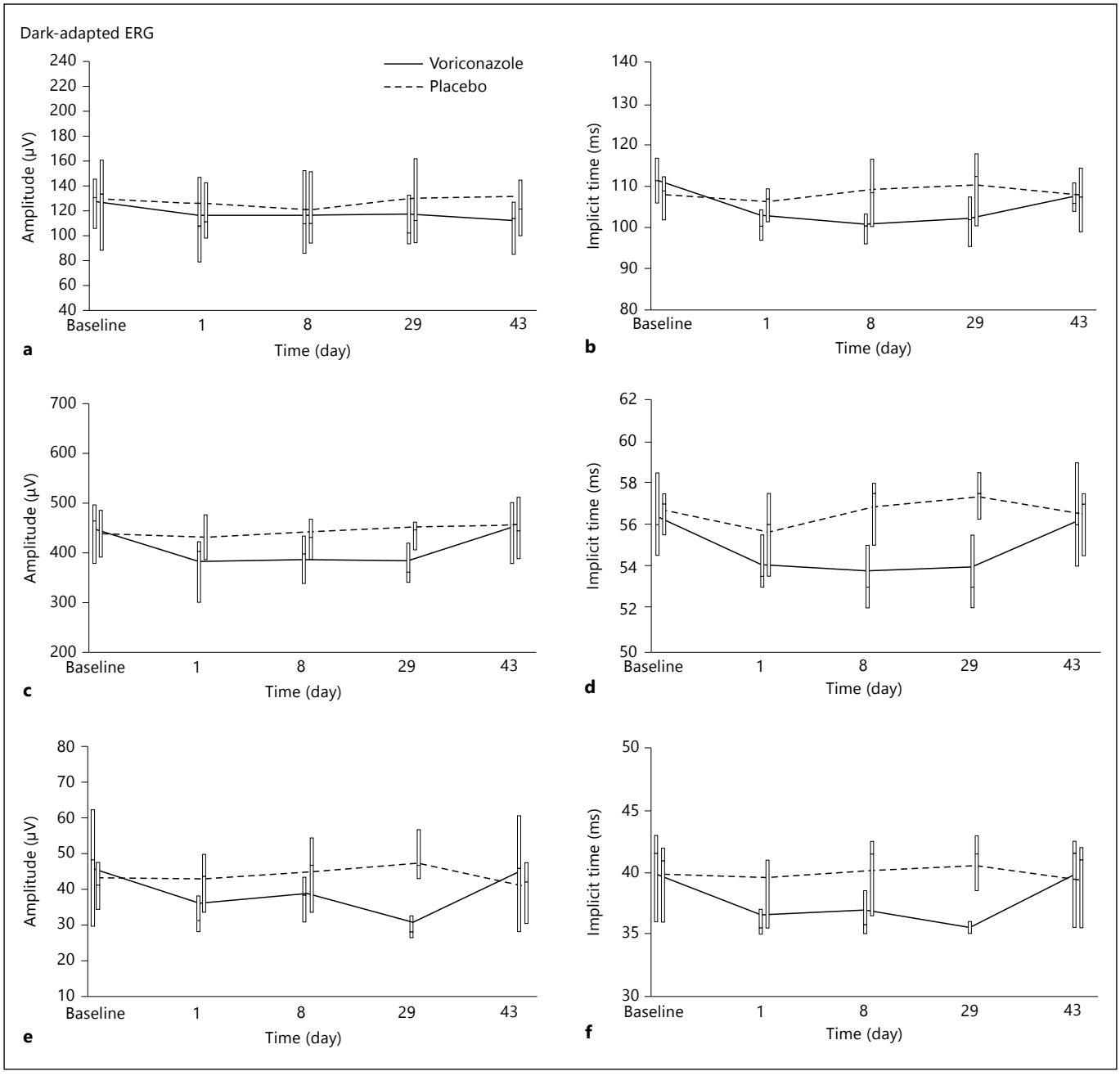
The mean age of volunteers was 32.1 years (range 19–46 years) in the voriconazole group and 26.3 years (range 20–43 years) in the placebo group. Mean trough plasma voriconazole concentrations ranged from 1,243–2,388 ng/ml; the concentration on day 7 was 2,388 (standard deviation 1,756) ng/ml, falling to 1,862 (1,273) ng/ml, 1,444 (987) ng/ml and 1,243 (844) ng/ml on days 14, 21 and 28, respectively.

Electroretinogram

ERG variables, which were amplitudes of b-waves, flicker responses in absolute values, and implicit times for the voriconazole and placebo groups at baseline and days 1, 8, 29 and 43, are presented in figure 1a–j.

Based on expert review of the data, the greatest attention was focused on the most technically robust ERG data in the study, i.e. the b-wave recordings elicited in step 2 by 3 cd s/m^2 (the so-called dark-adapted maximal response dominated by rods), and step 5 (the light-adapted flicker response reflecting cone function; fig. 2a–d).

Differences between voriconazole and placebo groups observed in step 2 b-wave amplitude across the 43-day observation period are shown in figure 2a based on the absolute mean amplitude values of both groups (fig. 1c). The screening-adjusted b-wave amplitude was 13% lower on day 1 in voriconazole-treated volunteers compared with volunteers receiving placebo ($p < 0.05$). The difference between these respective groups persisted during the treatment period of 29 days (day 8, 14% mean decrease; day 29, 17% mean decrease). By day 43, the screening-



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adjusted b-wave amplitude in the voriconazole group was similar to that of the placebo group (3% lower with voriconazole). Furthermore, the observed absolute mean b-wave amplitude on day 43 was similar to that observed at screening (fig. 1c). No marked changes in b-wave amplitude were observed in the placebo group.

From the analysis of step 2, the screening-adjusted a-wave amplitude was significantly smaller (less negative) in voriconazole volunteers than those receiving placebo between days 1 and 29 (amplitude reduction on day 1, 21%; day 8, 23%; day 29, 24%; fig. 3a). On day 43, the screening-adjusted voriconazole a-wave amplitude was comparable with the placebo amplitude (fig. 3a). As with the b-wave amplitude, the mean a-wave amplitude was similar at screening and day 43 (fig. 1c). The a-wave amplitude remained essentially unchanged in the placebo group.

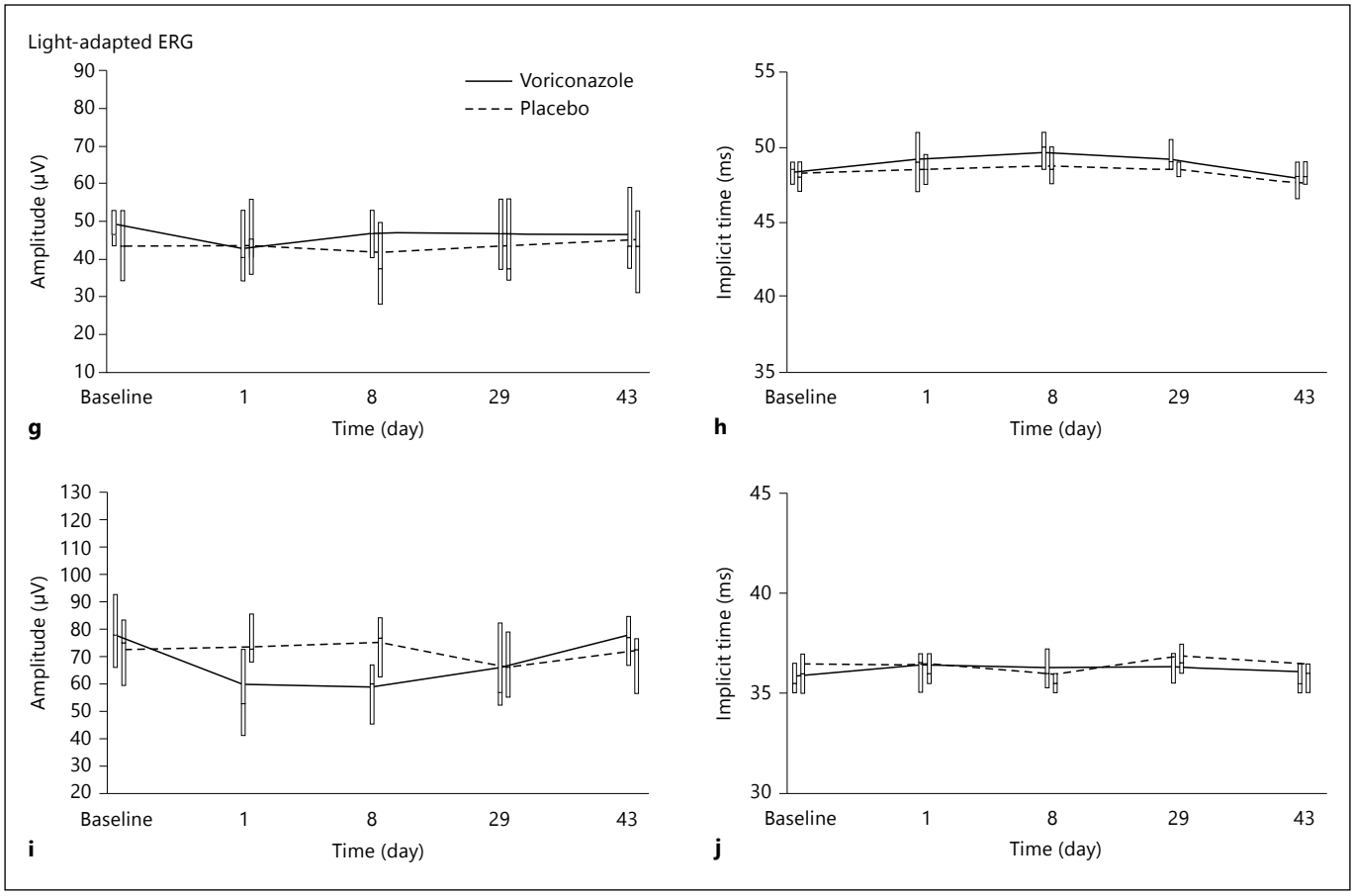

Fig. 1. ERG amplitudes and ERG implicit times of the dark-adapted ERG to: dim flashes (step 1, dark-adapted b-wave dim flash, 0.001 cd s/m^2; **a**, **b**), bright flashes (step 2, dark-adapted b-wave bright flash, 3 cd s/m^2; **c**, **d**) and filtered for oscillatory potentials (step 3, dark-adapted OP bright flash, 3 cd s/m^2; **e**, **f**) as well as responses in the light-adapted state (30 cd/m^2) for single flash cone responses (step 4, light-adapted b-wave bright flash, 3 cd s/m^2; **g**, **h**) and flicker responses (step 5, light-adapted flicker bright flash, 3 cd s/m^2) elicited by ganzfeld light stimuli of 3 cd s/m^2 (**i**, **j**). Boxes indicate 25th and 75th percentiles.

Similar results to step 2 were observed in step 3 OP amplitudes (fig. 1e). Screening-adjusted OP amplitudes on days 1, 8 and 29 were lower [by 19% (8.4 μV), 16% (7.4 μV) and 38% (17.2 μV), respectively] in volunteers treated with voriconazole compared with placebo; for days 8 and 29, this difference was statistically significant ($p < 0.05$). The screening-adjusted voriconazole OP amplitude was comparable with the placebo amplitude on day 43, even 7% larger. For placebo volunteers, absolute OP amplitudes remained similar between screening and day 43 (fig. 1e). The step 4 screening-adjusted photopic single flash cone response did not show any significant difference between groups (fig. 1g). The step 5 screening-adjusted photopic flicker response amplitude was significantly lower (by approx. 25%) on days 1 and 8 in volunteers receiving voriconazole versus placebo ($p < 0.05$; fig. 1i, absolute values and fig. 2c, relative differences compared with placebo group). By day 29, flicker response amplitudes were comparable between groups; similar results were observed on day 43. Additionally, the observed means on both days 29 and 43 were similar to those at screening (fig. 1i). Marked changes in amplitude were not observed in the placebo group during the study.

The implicit times for screening-adjusted step 2 b-wave amplitude in voriconazole-treated volunteers showed shortening of about 3–6% ($p < 0.05$) in comparison to the placebo group on days 1, 8 and 29 (fig. 2b). The step 2 a-wave screening-adjusted implicit time also showed a minor shortening (2%; $p < 0.05$) with voriconazole compared to placebo on days 1, 8 and 29 (fig. 3b). A shortening was also seen in the screening-adjusted implicit times of step 3 OP on days 1 and 8 (3.1 ms) and day 29 (5.0 ms) (fig. 1f).

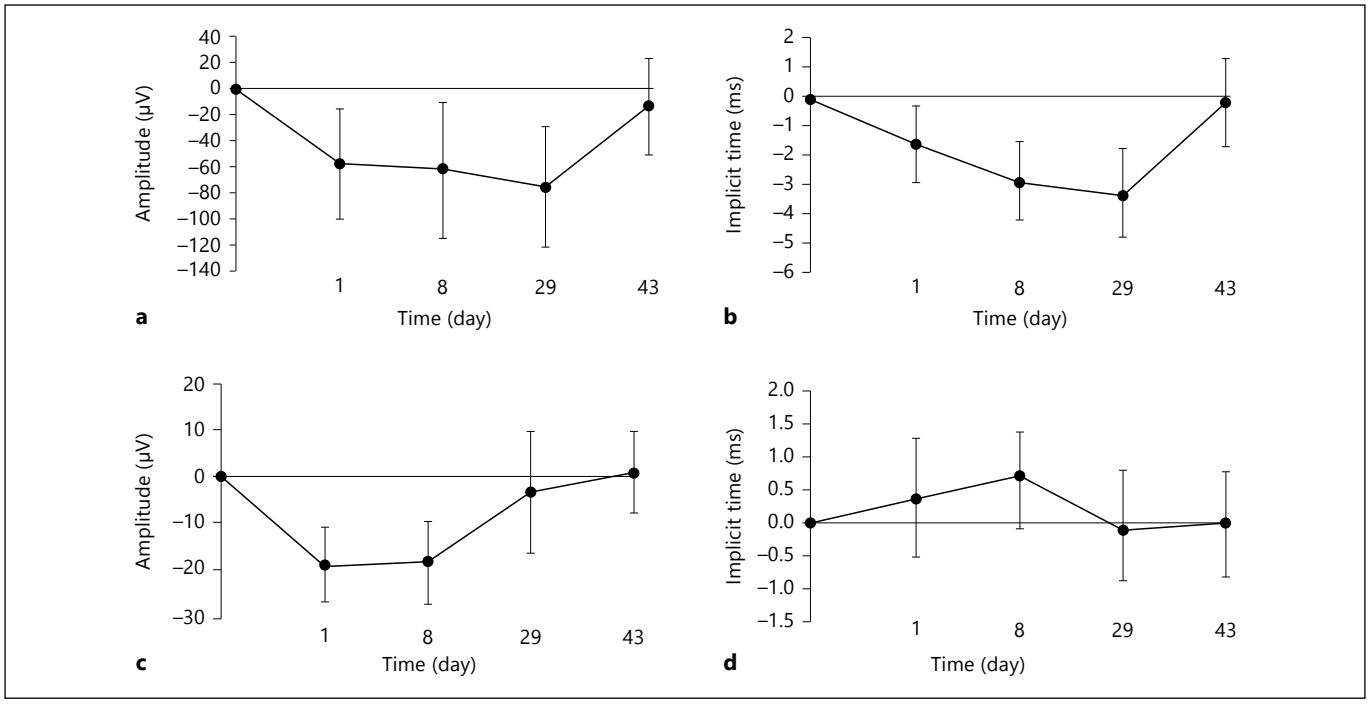

Fig. 2. Differences (means and 95% confidence intervals) between voriconazole and placebo groups in screening adjusted b-wave amplitudes and implicit times of dark-adapted step 2 (ISCEV standard flash 3 cd s/m^2) response (**a**, **b**) and light-adapted step 5 (30 Hz) photopic flicker (**c**, **d**). For all assessments and time points n = 17 except for: step 2 response (**a**, **b**), placebo, day 29 (n = 16); flicker amplitude (**c**), voriconazole, day 8 (n = 16); flicker time (**d**), voriconazole, day 8 (n = 16) and day 29 (n = 15).

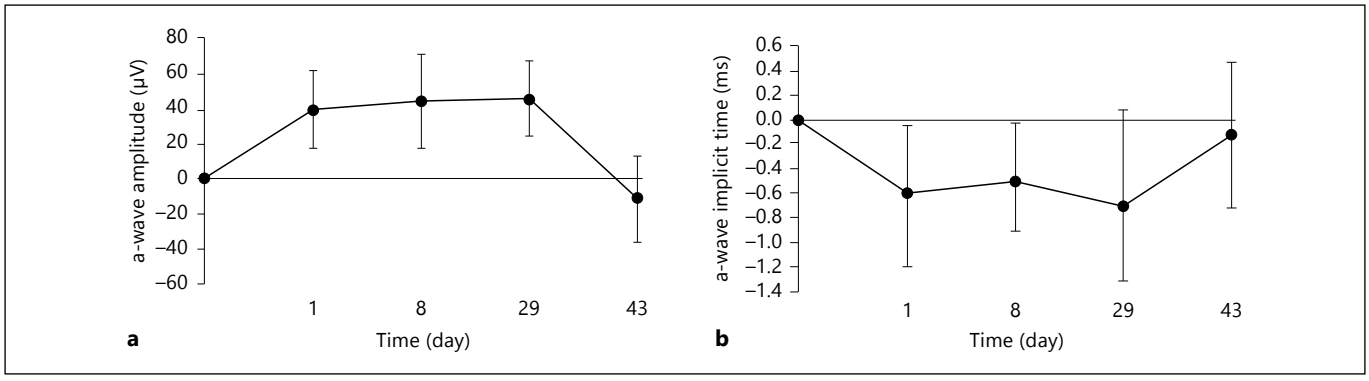

Fig. 3. Differences (means and 95% confidence intervals) between voriconazole and placebo groups in dark-adapted step 2 a-wave amplitude (**a**) and implicit time (**b**) elicited by ISCEV standard flash. Positive amplitude values indicate a decrease in the negative a-wave. For all assessments and time points n = 17, except placebo, day 29 (n = 16). Note that positive amplitude difference values indicate an amplitude decrease of the negative a-wave, when compared to placebo group (zero line).

No treatment group differences were observed on day 43 for step 2 b-wave (fig. 2b), step 2 a-wave (fig. 3b) and step 3 OP screening-adjusted implicit times (fig. 1f); furthermore, the observed absolute mean implicit times on day 43 were similar to those at screening. For the step 5 flicker peak time, there were small screening-adjusted, statistically nonsignificant mean prolongations, in the voriconazole group on days 1, 8 and 29 in comparison to placebo (fig. 2d). The b-wave amplitude and implicit time changes for step 1 (fig. 1a, b), technically of lower quality because

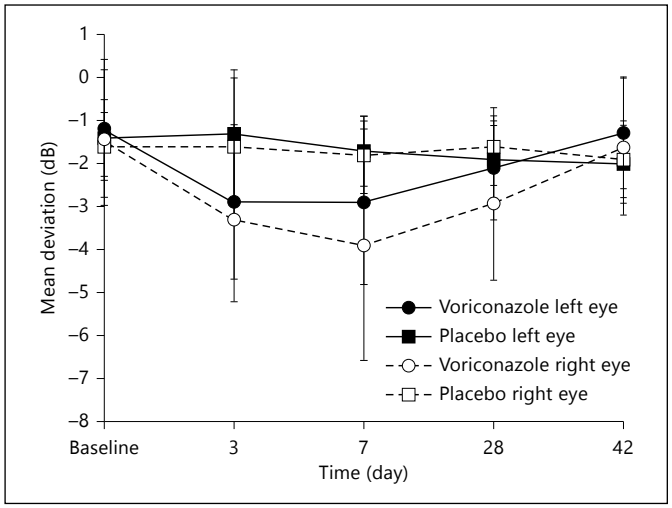

Fig. 4. Threshold to detect a light spot of increasing luminance in the Humphrey visual field test for all right and left eyes. The lowering of the threshold for detecting a dim light in the voriconazole-treated group indicates an increase in light sensitivity.

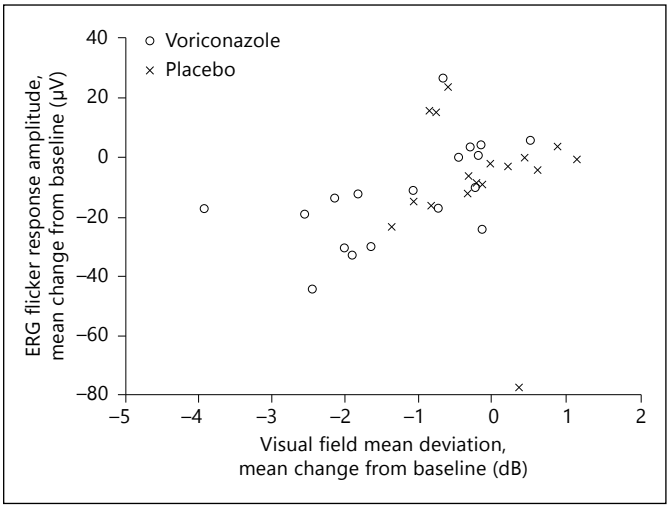

Fig. 5. Scatter plot of change of step 5 ERG flicker response amplitude versus mean deviation change in the Humphrey visual field testing on day 28/29. Points on the scatter plot represent values from individual volunteers.

of lower signal-to-noise ratio, were not statistically significant ($p > 0.05$) between treatment groups at any time point except implicit time on days 8 and 29.

FM-100 Hue Test

In the selected eye, the total error score increased from baseline in the voriconazole group, as seen on days 3 and 7 (table 1), despite the previously described learning effect [12]. Errors were most frequently located along a tritan axis. The mean total error score in the voriconazole group by day 42 was similar to placebo (table 1).

Humphrey Visual Field Test

Humphrey visual field test measurements revealed a decrease in mean deviation values during treatment with voriconazole and placebo compared to screening, up to –3.9 and –2 dB, respectively. Negative values indicate an increase in light sensitivity (fig. 4). The trend of increased light sensitivity was most marked on day 7, and some adaptation towards normal light sensitivity occurred between days 7 and 28. Pattern standard deviation remained unchanged (maximum mean increase 1 dB). Mean deviation and pattern standard deviation were stable in the placebo group throughout the study.

Other Visual Tests

Visual acuity was not affected, deteriorations of 2 or more lines were only observed with the placebo group. Two lines of variation in visual acuity can occur in normal

Table 1. Mean FM-100 hue test total error score measurements

	Voriconazole (n = 18)	Placebo (n = 18)
Screening	42.9 (25.0)	35.2 (27.4)
Baseline	33.8 (21.0)	21.3 (15.3)
Day 3	63.6 (33.8)	21.2 (15.6)[1]
Day 7	50.7 (28.0)	17.1 (10.6)
Day 28	37.6 (17.4)[1]	14.6 (15.2)[1]
Day 42	27.8 (15.6)[1]	20.2 (15.5)[1]

Figures in parentheses indicate standard deviations.
[1] n = 17.

volunteers without indicating pathology (e.g. depending on tear film variation, accommodative state concentration etc.). No abnormal changes were observed in the anterior or posterior eye segment in any volunteer, and pupil reflexes, accommodation and eye movements were found to be unaltered during voriconazole treatment.

Correlations between Tests

As visual field sensitivity showed a rather surprising tendency to increase in sensitivity, and as visual field assesses mainly cone system activity, the correlation between light sensitivity assessed by static visual field mean defect and ERG cone flicker amplitude was investigated (fig. 5). Interestingly, loss in amplitude in the voriconazole-treated group (circles) is accompanied by an in-

Table 2. Incidence (n) of treatment-related visual AEs

Visual AE	Voriconazole (n = 18)	Placebo (n = 18)
Enhanced/altered visual perception	9	3
Blurred vision	5	1
Changes in color vision	4	0
Photophobia	12	3
Other[1]	9	1
Total	15	5

[1] Included events relating to eye pain and abnormal vision.

crease in light sensitivity (threshold decrease), while data of placebo-treated volunteers (crosses) are clustered around the zero change point. No correlation was found with color vision discrimination ability in the FM-100 hue test.

Adverse Events

The majority of AEs were mild or moderate. Abnormal vision (77.8%; n = 14), headaches (66.7%; n = 12) and photophobia (66.7%; n = 12) were the most common AEs in the voriconazole group. AEs were transient in nature and reversible, and were not related to treatment duration. Fifteen volunteers in the voriconazole group experienced 1 or more treatment-related visual AEs compared with 5 in the placebo group (table 2). There were no discontinuations or serious AEs due to vision-related events. One discontinuation due to elevated γ-glutamyl transferase, alanine transaminase and aspartate transaminase on day 16 in 1 volunteer receiving voriconazole was classified as a discontinuation due to laboratory abnormalities and was recorded as a severe AE.

Discussion

Compared with both placebo and screening measurements, multiple oral doses of voriconazole resulted in reductions in the amplitude accompanied by shortening of implicit time of both the a-wave (fig. 3a, b) and the b-wave (fig. 2a, b) of the scotopic ERG, a rarely observed combination; in photopic ERGs, reduction of flicker response amplitude was accompanied by a slight but nonsignificant prolongation of implicit time. These changes were notable from day 1 but did not progress noticeably during the 4-week treatment period. On day 43, ERG waveform amplitudes had returned to screening values and were not different from placebo, suggesting that the effects of voriconazole on the retina are completely reversible.

Voriconazole caused a significant reduction in the amplitude of the maximum b-wave (step 2) in the dark-adapted state, a signal that originates from both rod- and, to a minor extent at higher stimulus luminances, from cone-driven cells in the retina. Significant amplitude reductions seen in step 5 (cone flicker response) suggest that voriconazole also affects retinal pathways of the cone system. In addition, the type of visual sensations reported following voriconazole treatment (increased sensitivity to brightness, dazzle or glare), in conjunction with the ERG data, including major changes in amplitude and implicit time of oscillatory potentials originating in the inner retina, suggests that voriconazole affects the interaction of the rod system with the cone system that is involved in light adaptation processes, rather than the cone system alone. This is supported by the observation that relative local contrast sensitivity, as assessed by static perimetry, increased slightly during voriconazole treatment, which may point to some disinhibition mechanism in the light-adapted state. The large amplitude loss seen in step 2 (maximal mixed rod and cone response) cannot be explained by loss of the cone system alone as cones contribute little to this response, suggesting that both rod and cone pathways are affected by voriconazole.

The lack of significant differences in the rod b-wave amplitude between the voriconazole-treated and placebo groups in step 1 does not conclusively exclude an effect of voriconazole treatment on the rod system, as the naturally lower signal-to-noise ratio of small b-wave amplitudes to dim light stimuli resulted in a larger confidence interval. Amplitude losses caused by degenerative or toxic processes are usually combined with implicit time prolongation. A drop in amplitude combined with shortening of implicit time is usually seen only when the neuronal circuitry of the retina is in a more light-adapted state [13], a condition that could eventually be mimicked by drug action on channels of retinal photoreceptors and/or neurons. An alternative hypothesis may be found in an action of voriconazole on horizontal cells, which control via the triad synapse the signal transmission from photoreceptors to bipolar cells during dark and light adaptation resulting in the formation of a syncytium that uncouples functional connections in the light-adapted state [14]. Such a mechanism could directly influence b-wave amplitude that reflects mainly the depolarization of on-bipolar cells [7]. Such changes in the mechanism of neural adaptation from a physiological perspective could also be

accompanied by perception of photophobia, dazzle and glare.

The precise mechanism of this action cannot be fully elucidated at this stage; voriconazole showed little affinity for D_1 and D_2 receptors, 5-hydroxytryptamine or the various γ-aminobutyric acid and N-methyl-D-aspartate binding sites, nor did it inhibit phosphodiesterase 6 [8]. The slight tritan defect in the FM-100 hue test, observed in voriconazole-treated volunteers, might indicate an increased susceptibility of the short wavelength cones to side effects of voriconazole. This is a common observation with neurotropic drugs [15, 16].

There was no indication of voriconazole-related neuronal dysfunction that would be typical of degeneration processes, nor did the funduscopy reveal signs of such degenerations, which in principle can be associated with amplitude decreases [16, 17]. The fact that significant implicit time prolongations of the b-wave in conjunction with ERG a- or b-wave amplitude losses were not observed suggests that voriconazole does not produce the typical signs of emerging retinal degeneration. In contrast, a significant shortening of implicit time was observed, especially of oscillatory potentials, which in conjunction with the reversibility of amplitude losses suggest a pharmacological effect of voriconazole on neuronal processing in the retina rather than a damaging toxicological effect; this notion is supported by the fact that the mean deviation in static visual field even decreased slightly during voriconazole treatment, indicating an increase in relative local contrast sensitivity across the visual field. It seems likely that voriconazole exerts a functional effect on the neuronal processing in the retina, which mainly affects neuronal adaptation control mechanisms; this would explain the observed changes in visual perception, but does not point to loss or permanent alteration of retinal neurons as the changes are fully reversible after treatment. Moreover, the transient subjective alterations induced by voriconazole are such that drug discontinuation was not indicated during the 28 days of oral dosing.

The frequency of visual AEs in this study was high compared to previous experience [1, 3–5]. In part, this reflects that the voriconazole dose was selected for its ability to yield plasma levels that are associated with visual effects [18]. Another possible reason for the high incidence of visual AEs is that the volunteers and investigators knew the study objective, and were therefore primed to recognize and record such events. In contrast, clinical trial patients may be less attuned to visual symptoms. Pooled data from previous voriconazole studies in patients and healthy volunteers show rates of altered or enhanced visual perception (32.2–38.3%) [8], which are close to that observed with voriconazole here. All visual disturbances induced by voriconazole had disappeared by day 43, 14 days after end of treatment, were transient, reversible, did not damage the retina and did not require treatment discontinuation.

In conclusion, there was no functional or morphological evidence that voriconazole causes any degenerative effects on the retina when given as multiple oral doses over 28 days. The effects of voriconazole on altered visual perception, ERG, color vision and static visual field thresholds are nonprogressive over a treatment period and reversible. It is hypothesized that voriconazole has a pharmacological effect on rod and cone pathways including a possible mechanism of disinhibition that reversibly puts the retina in a more light-adapted state and leads to increased relative contrast sensitivity.

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Erratum

To the article by Adamus G, Karren LJ, Mooney J and Burrows GG, entitled 'A promising therapeutic approach for treatment of posterior uveitis: recombinant T cell receptor ligand protects Lewis rats from acute and recurrent experimental autoimmune uveitis' [Ophthalmic Res 2010;44:24–33, DOI: 10.1159/000281815], the following Disclosure Statement is to be added:

OHSU and Dr. Burrows have a significant financial interest in Artielle Immunotherapeutics Inc., a company that may have a commercial interest in the results of this research and technology. This potential conflict of interest has been reviewed and managed by OHSU.