Acute electroretinographic changes during Sildenafil (Viagra) treatment for erectile dysfunction

Sildenafil-induced ERG changes

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Abstract

The authors describe their findings on 12 subjects who were treated with 50 mg of Sildenafil (Viagra) and underwent ERG measurements prior to and 1 hour after ingestion. The Naka–Rushton equation was used to describe the b-wave luminance-response function of the scotopic ERG. Statistically significant differences were noted in the $V_{\text{max}}$ and $K$ values. Sildenafil ingestion resulted in an increase in $V_{\text{max}}$ (higher rod response to light stimuli) and a decrease in $K$ (higher sensitivity).

Abbreviations: cGMP – cyclic guanosine monophosphate; PDE – phosphodiesterase; ROS – rod outer segment.

Introduction

Subjective reports of ocular adverse effects have been registered after oral ingestion of sildenafil: mild and transient, predominantly bluish tinge or haze to vision, but also increased sensitivity to light [1].

According to previous studies the incidence of abnormal vision increase with dosage: 3–11% in men taking recommended doses (25–100 mg), approximately 50% in men taking 200 mg, in all subjects (4/4 per group) taking 600 and 800 mg sildenafil [2, 3]. The visual symptoms usually peak 1–2 hour after taking the drug and disappear later.

Studies evaluating retinal function in humans by electroretinography have noted small transient changes to the ERG [4]. In particular, Vobig et al. reported a decrease in the a-wave and b-wave amplitude in the ERG of five healthy men 1 h after they took 100 mg sildenafil orally; the changes completely disappeared 5 h later [5].

The aim of the study was to evaluate acute electroretinographic (ERG) effects of 50 mg sildenafil ingestion by means of intensity amplitude function.

Materials and methods

Twelve subjects with a clinical diagnosis of erectile dysfunction of 6 months duration or longer volunteered the study (mean age was 53.5 ± 9.8 years). Inclusion criteria were no history of eye disease except refractive error (no more optical correction than five diopters of sphere or three diopters of cylinder), no history of diabetes mellitus or systemic arterial hypertension. We performed a complete ophthalmologic examination. All patients underwent ERG recordings according to ISCEV specifications [6].

Pupils were dilated with tropicamide 0.5% and phenylephrine 10% solutions. Before each recording session, all patients were dark adapted for 1 h. ERGs were recorded with Henkes-type corneal contact lens electrodes placed on right eye under dim red light after corneal anaesthesia with 2 drops of 0.4% oxibuproc-
ame chlorhydrate solution. A 0.5-Hz frequency white flash placed outside of the faradic cage, connected to a Ganzfeld dome by a fibre optic system was used to elicit the retinal signal, with a time window of 512 ms. The bandpass used for ERG recording was between 0.1 and 400 Hz. The recording procedure consisted in recording 25 iterations for each luminance level, starting 6 log units below the standard flash intensity (3 cd s/m²). Attenuation of the flash intensity was progressive, reducing the ND intensity by 0.3 log unit steps. Offline analysis allowed to run each data file through an artifact rejection process included in the software, to split sequential groups of the recorded samples and to average them separately. For ERG waveform analysis, the a-wave was measured from baseline to the first negative trough of the ERG response, and the b-wave amplitude was measured from the a-wave trough to the most positive peak of the response. At flash intensities that failed to evoke an a-wave, the b-wave was measured from baseline to the most positive peak. All implicit times were measured from flash onset to the corresponding a- and b-wave amplitudes. In so doing, the onset, growth and subsequent disappearance of the scotopic threshold response could be monitored, and thereafter rod b-wave amplitudes and latencies measured and to fit the Naka–Rushton equation analysis (Conel BDC, Computer System, software ver. 1.10, Rome, Italy). The Naka–Rushton equation of the form, \( V(I) = V_{\text{max}} I^\eta / (I^\eta + K^\eta) \), was used to describe the b-wave luminance-response function of the scotopic electroretinogram where \( V_{\text{max}} \) is the asymptotic value of the b-wave amplitude as a function of stimulus luminance \( I \), \( K \) is the luminance that produces a b-wave amplitude that is one-half \( V_{\text{max}} \), and \( \eta \) is a dimensionless constant that controls the slope of the function. Patients were examined 1 week before the study in a baseline observation. Best corrected visual acuity (BCVA) and ERG were repeated 1 h after 50 mg sildenafil ingestion.

The Local Ethics Review Committee approved the study. All patients gave fully informed written consent according to the Helsinki Declaration of human experimentation.

Statistical analysis was performed using one-way analysis of variance (ANOVA) fixed effects. Statistical significance level was set at \( p \leq 0.05 \).

Results

BCVA in all cases was 20/20 in both eyes. No significant alterations in morphological and functional parameters evaluated were detected.

Most relevant data are from ERG responses coming from intensity amplitude function. For statistical purposes we refer our data to right eyes. All subjects responded to sildenafil ingestion with a statistically significant shift towards higher levels in \( V_{\text{max}} \) (\( F(1,11)=20.98; p < 0.0008 \)) and with a significantly lowering in \( K \) (\( F(1,11)=32.19; p < 0.0001 \)). Mean increment in \( V_{\text{max}} \) at 1 hour was 23.3 \( \mu \text{V} \) (SD=17.62). With the exception of a subject who showed virtually no change (from 267.5 to 268.1 \( \mu \text{V} \)), in all subjects increment ranged from 5 to 21% of the baseline levels. \( K \) was 0.18 log unit (SD=0.11) smaller than baseline. \( \eta \) did not show relevant variations (\( F(1,11)=0.001; p < 0.9285 \)). (Figure 1 and Table 1)

In contrast, the amplitudes and implicit times of a- and b-waves at 1 hour after sildenafil administration were not significantly different from baseline (\( p > 0.05 \)).

Discussion

Sildenafil, which is mainly an inhibitor of phosphodiesterases-5 (PDE-5), also weakly inhibits PDE-6, which is actively present in retinal photoreceptors. Reported visual disturbances were interpreted as an inhibitory effect on the PDE-6.

Bleached rhodopsin activates a guanosine-binding protein which activates a rod outer segment (ROS) PDE, thereby inducing a light dependent decrease in cGMP concentration and consequently rods hyperpolarization. PDE inhibition normally occurs in the dark. The inhibited PDE highers the intracellular concentration of cGMP, leading to the opening of sodium channels and depolarization of the photoreceptors. We examined ERG variations by progressively increasing light stimulus intensities to reach the standard flash. The b-wave amplitudes as a function of stimulus luminance were fitted by the Naka–Rushton equation and the parameters \( V_{\text{max}} \), \( K \) and \( \eta \) were evaluated.

We used this approach to monitor alterations in retinal function since it can show selective changes in each parameter. This selectivity is an advantage over monitoring retinal function with single intensities or comparisons limited solely to ERG amplitudes. \( V_{\text{max}} \) is derived mathematically. It corresponds to the maximum rod response generated by the retina and is