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Evaluation of the acute effect of Sildenafil citrate on visual function in patients with early-stage age-related macular degeneration

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Abstract

• AIM: To assess the effect of a single dose of Sildenafil citrate on the visual function in men with early-stage age-related macular degeneration(AMD).

• METHODS: Forty men (mean age 71, range from 55-86 years) with early-stage AMD were prospectively randomized to receive either placebo or Sildenafil citrate (Viagra; Pfizer Inc, New York, NY) 100mg as a single oral dose. Subjects underwent visual acuity, Amsler grid and color discrimination in each eye before and at specific intervals within 9 hours after dosing.

• RESULTS: Compared with placebo, no pattern of errors were evident in any visual function test following Sildenafil administration. No statistically or clinically relevant changes from baseline were observed in visual acuity or color discrimination. No clinically relevant changes were observed in the Amsler grid. Sildenafil treatment was associated with transient mild or moderate headache and flushing.

• CONCLUSION: A single 100mg dose of Sildenafil was well tolerated and produced no significant acute visual effects in a sample of men with early-stage AMD.

• KEYWORDS: Sildenafil citrate; visual function; age-related macular degeneration
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INTRODUCTION

Cyclic guanosine monophosphate (cGMP)-DE-pendent phosphodiesterase type 6 (PDE6) is present in high concentrations in cone and rod cells and plays a key role in retinal light signal photo transduction. Activated PDE6 hydrolyzes cGMP to effect a reduction in cGMP concentration in the outer segments of rods and cones. This reduction in cGMP triggers the sequential closure sodium channels resulting in hyper-polarization of the photoreceptors, release of neurotransmitter, and propagation of visual signals to post synaptic cells[1]. Sildenafil citrate (VIAGRA; Pfizer Inc, New York, New York) is effective in treating erectile dysfunction by selectively inhibiting cGMP-dependent PDE5 in corpus cavernosum smooth muscle cells[2]. It also weakly inhibits PDE6, reflecting an affinity for PDE6 that is one tenth of its affinity for PDE5[3]. Therefore, the potential for Sildenafil to produce visual effects secondary to PDE6 inhibition was evaluated during its clinical development. As documented in double-blind placebo-controlled phase II studies in healthy male volunteers and patients with erectile dysfunction, no clinically significant changes in visual acuity, intraocular pressure(IOP), contrast sensitivity, photo-stress test, or pupillometry measurements and minimal changes in electroretinograms (ERGs) were observed at Sildenafil doses ranging from 50-200mg, compared with placebo[4,5]. Overall, abnormal vision, described as mild occurrences of a transient blue tinge to vision or as increased brightness of or sensitivity to lights, was reported by 3% of patients receiving 50mg doses and 11% of patients receiving 100mg doses of Sildenafil in phase II/III clinical trials[6]. Color vision testing using the Farnsworth-Munsell 100-hue (FM 100-hue) test indicated that modest transient abnormalities in color vision, particularly in the blue-green range, occur predominantly at the maximum recommended dose of Sildenafil (100mg) or at twice the highest recommended dose (200mg)[1,4,5].

Patients with early stages of macular degeneration, defined as minimal visual impairment and large drusen in the macula, have partial impairment of visual function (including visual acuity, contrast sensitivity, and color vision)[7]. Thus, inhibition of PDE6 could theoretically exacerbate visual difficulties in subjects with macular degeneration. Additionally, since age-related macular degeneration (AMD) becomes more frequent over the age of 60, many elderly patients receiving Sildenafil treatment for erectile dysfunction undoubtedly also have some degree of macular degeneration. Although visual function is partially compromised in this patient group, it is still measurable and sufficient enough to provide meaningful qualitative and quantitative information[8]. We therefore conducted this study to assess the effect of a single dose of Sildenafil citrate on the visual function in men with early-stage AMD.

MATERIALS AND METHODS

Forty male subjects aged 55 years or older with documented early-stage AMD characterized by coalescent soft drusen, who had corrected visual acuity of 20/40 or better in at least one eye were chosen from the out patient clinic of the Research Institute of Ophthalmology Giza, Egypt within the period between February 2006 and May 2008.

Subjects were excluded if they had taken nitrates during the previous 3 weeks or any other drugs known to affect visual function within 1 month before the start of the study. Subjects were also excluded if they had eye disorders other than macular degeneration, including diabetic retinopathy, retinal detachment, cataract or glaucoma requiring treatment, color blindness, or corrected visual acuity of 20/50 or worse.

Subjects were randomized to double-blind treatment with a single dose of either placebo or Sildenafil 100mg. Study drug doses were taken between 8am-10am, at least 1 hour after a light breakfast with 240mL of water. Subjects were not allowed to take any other drug known to affect visual or retinal function for the duration of the study.

The effects of Sildenafil on visual function were assessed using a battery of visual function tests performed in the following order visual acuity, Amsler grid test and color discrimination. Subjects completed all visual tests in each eye, starting with the eye with the better visual acuity (or the right eye if acuity was identical) 1 hour before dosing then 1, 5 and 7 hours post-dose.

Best-corrected visual acuity (BCVA) was assessed for each eye using Snellen chart at a distance of 6m. The smallest line on which the majority of letters could be read by each eye was recorded. A change from the pre-dose (baseline) value was determined in each eye and classified as deterioration, improvement, or no change in visual acuity at each post dose assessment. Improvement or deterioration was defined as a change of at least two lines.

While viewing the Amsler grid, the subjects were asked to assess whether their vision was normal. If not, they were asked whether they noted a central or peripheral scotoma or distortion of vision (metamorphosia). A change from pre-dose during the Amsler grid test for each eye was classified as worse, better, or the same at each post-dose assessment.

The subjects were also asked for color discrimination by the Pseudo-Isochromatic Plates using Ishihara color blindness test to get an idea of subjects color efficiency or deficiency.

RESULTS

The median visual acuity scores following treatment with Sildenafil or placebo did not change significantly from pre-dose scores and there was no clinically relevant difference between treatments. The median scores for the right eye were 6/9 before Sildenafil dosing and 6/9 and 6/6, respectively, at 5 and 7 hours after Sildenafil dosing. The median scores for the left eye were 6/9 before Sildenafil dosing and 6/9 and 6/9, respectively, at 5 and 7 hours after Sildenafil dosing. In comparison, the median scores for the right eye were 6/9 before placebo dosing and 6/6 and 6/6, respectively, at 5 and 7 hours after placebo dosing. For the left eye, the median scores were 6/18 before placebo dosing and 6/9 and 6/9, respectively, at 5 and 7 hours after placebo dosing. All subjects showed no change in visual acuity following treatment with Sildenafil. Two subjects showed an improvement in visual acuity following placebo.

Pretreatment results for Amsler grid test in the right eye indicated normal vision in thirty six subjects and abnormal vision due to metamorphopsia in four subjects. The vision of all subjects that were normal remained normal following Sildenafil treatment. One subject with abnormal findings showed increased metamorphopsia at 1, 5, and 7 hours after Sildenafil dosing.

Pretreatment results of the Amsler grid test for left eye indicated thirty five subjects with normal vision and five with abnormal vision due to metamorphopsia. The vision of all that were normal remained normal following treatment with Sildenafil. The five with abnormal Amsler grid findings, one subject had better vision 5 hours after and one subject had worse vision 7 hours after receiving Sildenafil. There was no evidence that these changes were related to Sildenafil treatment. Following treatment with placebo, the Amsler grid findings of all subjects were the same as in the pre-dose period for both right and left eyes.

No significant or clinically relevant differences between treatments were observed for color discrimination suggesting a lack of additional effect of Sildenafil on the subjects' ability to distinguish colors.

Independent of the visual test measurements, there were no visual disturbances reported. So no visual disturbance questionnaires were completed. There were no laboratory test abnormalities related to study drug administration or clinically significant changes in blood pressure or pulse rate.

DISCUSSION

In addition to its inhibitory effect on PDE5, the target enzyme for therapeutic efficacy in patients with erectile dysfunction, Sildenafil exerts a minor inhibitory effect on PDE6. Because PDE6 plays an important role in retinal photo transduction, its partial inhibition may account for the infrequent occurrence of visual effects observed in flexible dose controlled clinical trials of Sildenafil in men with erectile dysfunction[8,9]. Some concerns have been expressed about the use of Sildenafil by individuals with preexisting retinal disorders and its possible effects on their visual function. In the present study, treatment with a single maximum recommended dose of Sildenafil (100mg) produced no acute visual effects compared with placebo in a group of forty men with early-stage AMD and some degree of reduced visual acuity.

No clinically relevant changes from baseline in visual function in either the right or left eye were observed, as assessed by a battery of visual function tests. Furthermore, there was no evidence of a discernible pattern of errors in any visual test as a function of time after dosing with Sildenafil nor a consistent pattern of errors within one subject. Bearing in mind the inherent limitations conferred by the small number of study patients, in clinical practice, the lowest effective dose of Sildenafil should be prescribed for patients with AMD.

The results of this study are consistent with the results of a retrospective analysis of data from a subgroup of 66 participants in phase II/III studies who had both erectile dysfunction and a history of eye disorders, including diabetic retinopathy, glaucoma, and macular degeneration[10]. That analysis showed little evidence of a trend toward an increase in visual adverse events AEs during treatment with fixed or flexible doses of Sildenafil ranging from 5mg to 200mg($n=39$) or placebo ($n=27$) for 4-26 weeks. The incidence of visual AEs in the patients receiving Sildenafil was 6/39 (15%) and in patients receiving placebo was 2/27 (7%).

The current study is only representative of visual safety following a single dose. There are some reports that have looked at visual function after long-term intermittent dosing with Sildenafil in patients with erectile dysfunction. Consistent with our findings, Zrenner *et al* [5] found no clinically significant changes from baseline in visual acuity, contrast: sensitivity, or photo-stress tests following administration of Sildenafil at doses of 50 to 200mg for 12 weeks, followed by doses of 25mg to 100mg for 40 weeks on an as-needed basis in men with erectile dysfunction. The most frequently reported AEs (flushing, rhinitis, and headache) are well known AEs of Sildenafil that are usually mild-to-moderate in severity[6]. Open-label long-term extension studies have not revealed any increase in ocular-related AEs or any unusual ocular AEs that were not reported during double-blind clinical trials[11]. Further reassuring post-marketing data have been obtained from a variety of sources, including new clinical research studies, spontaneous reports, surveillance studies, epidemiologic studies, and the National Registry of Drug Induced Ocular Side Effects[12]. However, testing of visual function after long-term treatment with Sildenafil has not been performed prospectively in subjects with eye disorders.

The most common type of visual AE, blue-green color discrimination occasionally reported at higher doses of Sildenafil, was examined in some detail in a phase II study. In a double-Wind placebo-controlled crossover trial in 16 healthy male volunteers, significant changes in FM 100-hue scores were observed only at 1 or 2 hours after a single acute dose of Sildenafil[4]. At 1 hour, mean FM 100-hue total error scores were 75 ± 40 for 100mg and 102 ± 56 for 200mg, compared with a placebo score of 53 ± 36 ($P<0.05$). At 2 hours, the total error score for subjects receiving 200mg Sildenafil was 99 ± 64 compared with 56 ± 33 for subjects receiving placebo ($P<0.05$). No significant changes were measured at 4 hours post-dose. These changes were regarded as mild, transient, and fully reversible occurrences that coincided with the time of the peak plasma drug concentration[4]. The effects of Sildenafil on blood flow in the eye could have important implications for patients with AMD or other eye disorders. Published reports thus far have indicated that Sildenafil has no significant effect on intra ocular pressure[13,14]. The effects on the ocular circulation specifically have, to this point, been variable. Grunwald *et al* [15] have reported no significant changes in choroidal or optic nerve head blood flow after acute doses of 100mg Sildenafil, whereas Sponsel *et al* [16] reported a significant increase in pulsatile ocular blood flow. Hence, the vasodilatory properties of Sildenafil do not seem to be producing a decrease in ocular blood flow. However, there are isolated case reports of nonarteritic anterior ischemic optic neuropathy (AION) in the literature since Sildenafil became available for clinical use in the United States[16,17]. In controlled clinical trials, no cases of AION were reported during 11 000 person-years of exposure to Sildenafil[18]. Clear attribution has been difficult, because AION is the most common acute optic nerve disorder among middle-aged and elderly adults. In most cases, risk factors such as predisposing illness, diabetes mellitus, hypertension, or an anatomic risk factor such as a small optic nerve head (disk at risk) has been present. Certainly, the appearance of these cases warrants careful monitoring to detect any emerging pattern.

In 2004 Herbert and associates investigated short-term visual effects of a single oral 100mg dose of Viagra in healthy young men. The single dose led to small but statically significant transient changes of outer and inner retinal function, as detected by ERG and psychophysical methods. Although the acute effects were fully reversible within 24 hours, it would be worthwhile to compare them with those induced by other PDE5 and PDE6 inhibitors[19]. Favorable results from the current study showed that there were no significant acute changes in visual function after a single dose of Sildenafil in a sample of men with early-stage AMD which were similar to David and associates who studied the effect of a single 100mg dose of Sildenafil and came to the conclusion that it was well tolerated and produced no acute visual effects or exacerbation of preexisting visual impairment in nine men with early-stage AMD[20].

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评价枸橼酸西地那非片对早期 AMD 患者视功能的急性效应

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摘要

目的:评估单剂量枸橼酸西地那非片对早期年龄相关性黄斑变性(AMD)男性患者视功能的急性效应。

方法:早期年龄相关性黄斑变性男 40 例,年龄 58~86(平均 71)岁,前瞻性随机接受安慰剂或者枸橼酸西地那非片(Viagra; Pfizer Inc, New York, NY) 100mg,单次口服。受试者双眼在接受药物之前及之后 9h 内特定的时间间期进行视力、Amsler 方格表及辨色力检查。

结果:与安慰剂相比,服用枸橼酸西地那非片后视功能检查均未有明显改变。视力和辨色力检查在基线水平上未见有统计意义或临床相关的改变,Amsler 方格表检查未见临床相关的改变。服用枸橼酸西地那非片与短暂的轻度至中度头痛和面红有关。

结论:单次口服 100mg 枸橼酸西地那非片,在早期年龄相关性黄斑变性男性样本人群中,耐受性良好,未对视觉产生显著急性效应。

关键词:枸橼酸西地那非片;视功能;老年黄斑变性