REVIEW ARTICLE

The use of multifocal electroretinography in the assessment of retinal toxicity caused by pharmacological agents

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Abstract

Multifocal electroretinography has found a role in the detection of ocular drug toxicity over the past 15 years. This review summarises how multifocal electroretinography has been used to evaluate the retinal toxicity caused by various ocular as well as systemic pharmacological agents. The use of multifocal electroretinography for monitoring the recovery of retinal function after withdrawal of the offending drugs is explored, as is the use of this technique to assess the efficacy of strategies to reduce retinal drug toxicity. Further developments in multifocal electroretinography to improve the detection of retinal toxicity in the future are also discussed.

Key words: Drug toxicity; Electroretinography; Photochemotherapy

Introduction

Multifocal electroretinography (mfERG) was developed by Sutter and Tran[1] and has since revolutionized objective functional assessment of retinal diseases. In contrast to full-field electroretinography (ERG), which measures the electrical activity of the entire retina, mfERG allows simultaneous measurements of multiple responses at different retinal locations, thus enabling topographic mapping of retinal function in the central 40-50 degrees of the retina. This review aims to provide an overview of the currently available literature on the use of mfERG in the assessment of retinal dysfunction associated with various ocular and systemic pharmacological agents.

The use of multifocal electroretinography in assessing retinal dysfunction due to ocular pharmacological agents

Photodynamic therapy with verteporfin

Randomized controlled trials demonstrate that photodynamic therapy (PDT) with verteporfin is effective in the treatment of subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD),[2] myopic CNV,[3] and central serous chorioretinopathy (CSC).[4,5] Several studies have used mfERG to provide an objective assessment of retinal functional changes after PDT.[6-14] In the study by Palmowski et al,[7] there was improvement in parafoveal function after PDT as reflected by central visual field testing as well as mfERG recordings, the latter being performed at intervals of 2 to 14 weeks (mean interval, 7 weeks) after PDT. Lim et al[14] compared the use of PDT and focal thermal laser photocoagulation in the treatment of CSC. Gradual improvements in mfERG responses were noted over the ensuing 6 months, but there was no significant difference between the 2 groups. In another study which focused on long-term results after PDT, Moschos et al[8] demonstrated increase in retinal response densities 6 months after PDT to treat myopic CNV. In another study,[9] however, the same authors found reductions in mean retinal response densities in the foveal and parafoveal areas 6 months after PDT for

AMD. Similarly, Rüther et al[10] found a general reduction in P1 response amplitude and a delay in the implicit time after a median interval of 6 weeks post-PDT, but the differences between the baseline and 6-week P1 response amplitude and implicit time were not statistically significant. These studies showed that various forms of functional changes at the macula can occur in patients having PDT for CNV. However, these studies were not aimed at investigating early changes in retinal function after PDT, as the follow-up mfERG recordings were performed at variable intervals after PDT such that short-term effects on retinal function could not be assessed.

The side-effects of PDT include transient visual disturbances that develop shortly after the treatment. Being subtle and non-specific changes, they are often difficult to detect objectively by visual acuity testing alone. mfERG has been performed to investigate these short-term changes in macular function. Jiang et al[6] evaluated mfERG findings 3 and 7 days after patients had PDT for CNV. It was shown that with exception of a statistically significant delay in N1 implicit time for ring 5 seven days post-PDT, no other significant changes were encountered. Lai et al[11] also used mfERG to evaluate acute changes in macular function after PDT, and demonstrated a transient reduction in macular function on day 4 post-treatment. In another study by Tzekov et al,[12] mfERG was performed in primates before and after PDT with verteporfin. The treatment resulted in 70 to 80% reduction in response amplitudes in the first week post-PDT. Imai et al[13] also evaluated the changes in retinal functions after PDT for AMD and polypoidal choroidal vasculopathy, and reported significant reductions in P1 response amplitudes at week 1 post-treatment. Whereas, compared to baseline no significant changes in mfERG response amplitudes were demonstrable 3 months later. These findings showed that PDT with verteporfin may result in retinal dysfunction that could explain early subjective visual disturbances encountered after PDT in the presence of normal clinical findings. Such mfERG findings can also be a useful guide for optimizing the treatment parameters so as to minimize potential side-effects following PDT. Paskowitz et al[15,16] performed studies on rats to investigate neurotrophic factors that could potentially reduce the retinal toxicity caused by PDT. Intravitreal injection of brain-derived neurotrophic factor (BDNF) into the eyes of rats 2 days before PDT preserved mfERG responses 1 week later. They also reported that BDNF did not interfere with the therapeutic effect of PDT on the choroidal circulation as seen on fluorescein angiography.

Intravitreal bevacizumab

Bevacizumab is an anti–vascular endothelial growth factor licensed for use in the treatment of colon cancer. Off-label uses in ophthalmology as intravitreal injections include the treatment for diseases such as CNV and macular edema secondary to retinal vein occlusion. Numerous studies have assessed the changes in mfERG responses after intravitreal bevacizumab injection.[17-22] Maturi et al[17] assessed mfERG changes in 4 patients with AMD who received intravitreal bevacizumab; assessments were performed at baseline and 1 month post-injection. All patients enjoyed improvement in mfERG response density of the central macula. Moschos et al[18] also studied patients who received intravitreal bevacizumab for the treatment of AMD. They evaluated 18 eyes with CNV secondary to AMD after receipt of bevacizumab injections and found that at 1 month, mfERG response density of the central area had increased compared to baseline, but there was no significant difference in the response at 3 months. In another study by Moschos et al,[19] 10 eyes with macular edema secondary to central retinal vein occlusion that treated with bevacizumab were assessed by mfERG. They reported that responses showed significant improvement compared to baseline at 1 month and 3 months. Shetty et al[20] assessed the mfERG findings in patients with macular edema secondary to retinal vein occlusion and diabetic macular edema who received intravitreal bevacizumab. In all 17 patients, when compared to baseline the mfERG P1 amplitudes at the central 20 degrees showed significant increases at 2 months. In a prospective study of 26 eyes by Pedersen et al,[22] mfERG was performed at baseline, 1 week, 6 weeks, 3 months and 6 months after bevacizumab injection. P1 amplitudes improved significantly from baseline at all time-points. These authors also performed full-field ERG, which showed a decrease in a-wave amplitudes and b-wave implicit times, of the single-flash cone response at 3 months. The 30-Hz flicker amplitudes were also reduced at 3 months. However, these changes normalized at 6 months. Karanjia et al[21] correlated mfERG responses with retinal locations that were involved or uninvolved in the disease process. After bevacizumab injection, they found that there was significant increase in the P1 response in disease-involved areas, while the response remained unchanged in areas without lesion. These results indicate that intravitreal bevacizumab does not confer any toxic effect to the retina demonstrable by mfERG.

Silicone oil for retinal detachment

mfERG has been used to investigate the changes in retinal function before and after retinal detachment surgery.[23-25] Since it allows separate assessment of retinal function between the attached and detached retina, mfERG has offered an advantage compared to full-field ERG. Occasionally, unexplained visual loss follows retinal detachment surgery, for which mfERG would be useful in the evaluation of retinal dysfunction. Cazabon et al[26] performed mfERG to evaluate unexplained visual loss after silicone oil removal in 3 patients who had vitrectomy for retinal detachment, and demonstrated reduced responses at the central macula that correlated with the reductions in the pattern of ERG amplitudes. The exact mechanism of visual loss remained uncertain. Nonetheless the mfERG findings provided evidence that macular dysfunction might ensue after silicone oil tamponade for retinal detachment.

Trypan blue staining in epiretinal membrane surgery

Intraoperative application of trypan blue dye has been used to facilitate the removal of epiretinal membrane, by

providing a better contrast for visualization. mfERG has been used to assess potential macular dysfunction after epiretinal membrane surgery with trypan blue staining. Balayre et al[27] performed mfERG recordings in 7 patients with epiretinal membranes 1 week before and 1 and 4 months after surgery. They found that the application of 0.2 ml of 0.15% trypan blue during surgery facilitated epiretinal membrane removal, nor did it cause significant changes in postoperative mfERG responses. However, the sample size was rather small and there was no control group for comparison. Further studies to evaluate potential retinal toxicity associated with intraoperative application of trypan blue during epiretinal membrane surgery might therefore be useful.

Indocyanine green staining in internal limiting membrane peeling surgery

Indocyanine green (ICG) has been used as a stain to facilitate internal limiting membrane (ILM) peeling. mfERG has been used to detect macular dysfunction after the use of ICG in macular surgery. Ferencz et al[28] compared the mfERG responses in patients with idiopathic macular holes who underwent pars plana vitrectomy and ILM peeling with or without the use of ICG. At postoperative months 3 and 6, both groups revealed reductions in mfERG responses compared to those at baseline. At 20 months post-surgery, both groups showed increases in mfERG responses in the central retinal area. In the group in which ICG was not used, the increase was more significant. Better outcomes without the use of ICG suggest possible dye toxicity. In a randomized controlled trial by Lai et al,[29] 13 patients undergoing epiretinal membrane and ILM peeling surgery were randomized to receive either 0.5 mg/ml or 1.25 mg/ml of ICG. mfERG recordings were performed in all patients at baseline and at 3 and 6 months postoperatively. At 3 months after surgery, the former group showed no change in mfERG responses compared to baseline. In the 1.25 mg/ml group, there were significant reductions in N1 and P1 response amplitudes compared to baseline values. Six months after surgery, both groups showed no significant changes in mfERG responses compared to those at baseline. These results suggest that higher concentrations of intraoperative ICG might cause transient retinal functional impairment.

The use of multifocal electroretinography in assessing retinal dysfunction due to systemic pharmacological agents

Chloroquine and hydroxychloroquine

Anti-malarial drugs such as chloroquine (CQ) and hydroxychloroquine (HCQ) are commonly used in the treatment of connective tissue diseases. Irreversible retinal toxicity may be associated with long-term use of these drugs by causing the development of annular (bull's eye) maculopathy. mfERG has been used in the assessment of CQ and HCQ retinal toxicities (**Figure 1**). Characteristically mfERG findings specific to CQ and HCQ retinal toxicity manifest as parafoveal reduction in P1 response amplitudes and delays in N1 and P1 implicit times.[30-46] Using mfERG, it is evident that long-term HCQ therapy lead to retinal functional abnormalities despite normal visual acuity and absence of fundal abnormalities.[32,34-36,39-41]

So et al[35] demonstrated pericentral depression in mfERG response amplitudes in 3 (50%) of the 6 patients who had been on HCQ for more than 5 years. In another study by Maturi et al[31], mfERG abnormalities were noted in 11 (58%) of 19 patients on long-term HCQ therapy. All except 1 patient had normal Amsler grid test findings and color vision. The authors identified 4 patterns of mfERG amplitude abnormalities, including: paracentral loss, foveal loss, peripheral loss and generalized loss. The evolution of HCQ retinopathy was demonstrated in 1 patient and there was gradual prolongation of P1 implicit times during follow-up. Results from these studies demonstrated that retinal dysfunction is common in patients on long-term HCQ therapy. Tzekov et al[36] also performed mfERG in several patients on HCQ and observed abnormalities in patients with reduced full-field ERG and bull's eye maculopathy. Nebbioso et al[40] has compared the use of mfERG and full-field ERG in the assessment of HCQ toxicity. In their cross-sectional study of 50 such patients, mfERG revealed abnormalities in 70% of clinically asymptomatic eyes, whereas full-field ERG only detected abnormalities in 16%. Thus, mfERG appeared to be more sensitive than full-field ERG in the detection of HCQ toxicity, and could possibly be used to enable documentation of preclinical HCQ retinopathy.

Moschos et al[33] also showed that 8 (40%) of the 20 patients, who had been on HCQ treatment for less than 5 years, nevertheless had mfERG abnormalities. HCQ use was discontinued in patients who had severe reductions in mfERG responses and the abnormalities returned to normal in some of the patients. Other studies have also demonstrated the improvement of mfERG responses after cessation of HCQ, in patients with suspected HCQ retinopathy.[32,42,43] These findings suggest that retinal dysfunction caused by HCQ is potentially reversible.

Although the sites of HCQ toxicity are commonly believed to be at the retinal pigment epithelium (RPE) and photoreceptor levels; the exact mechanism of toxicity remains uncertain. Furthermore, HCQ may be toxic to the retinal ganglion cells. To investigate the effects of HCQ on inner retinal function, Penrose et al[34] used a special mfERG stimulus to measure the second-order response, which evaluated adaptation behavior of the retina in patients taking HCQ. This protocol allowed earlier detection of focal abnormalities in HCQ retinopathy. However, some patients had abnormal first-order mfERG responses to the classic mfERG stimulus, despite having normal second-order response to the new stimulus. Thus, the use of this stimulus for assessing HCQ retinopathy requires further evaluation.

In the cross-sectional study by Lai et al,[44] it was demonstrated that mfERG response amplitudes correlated significantly with both the cumulative dose of HCQ and the

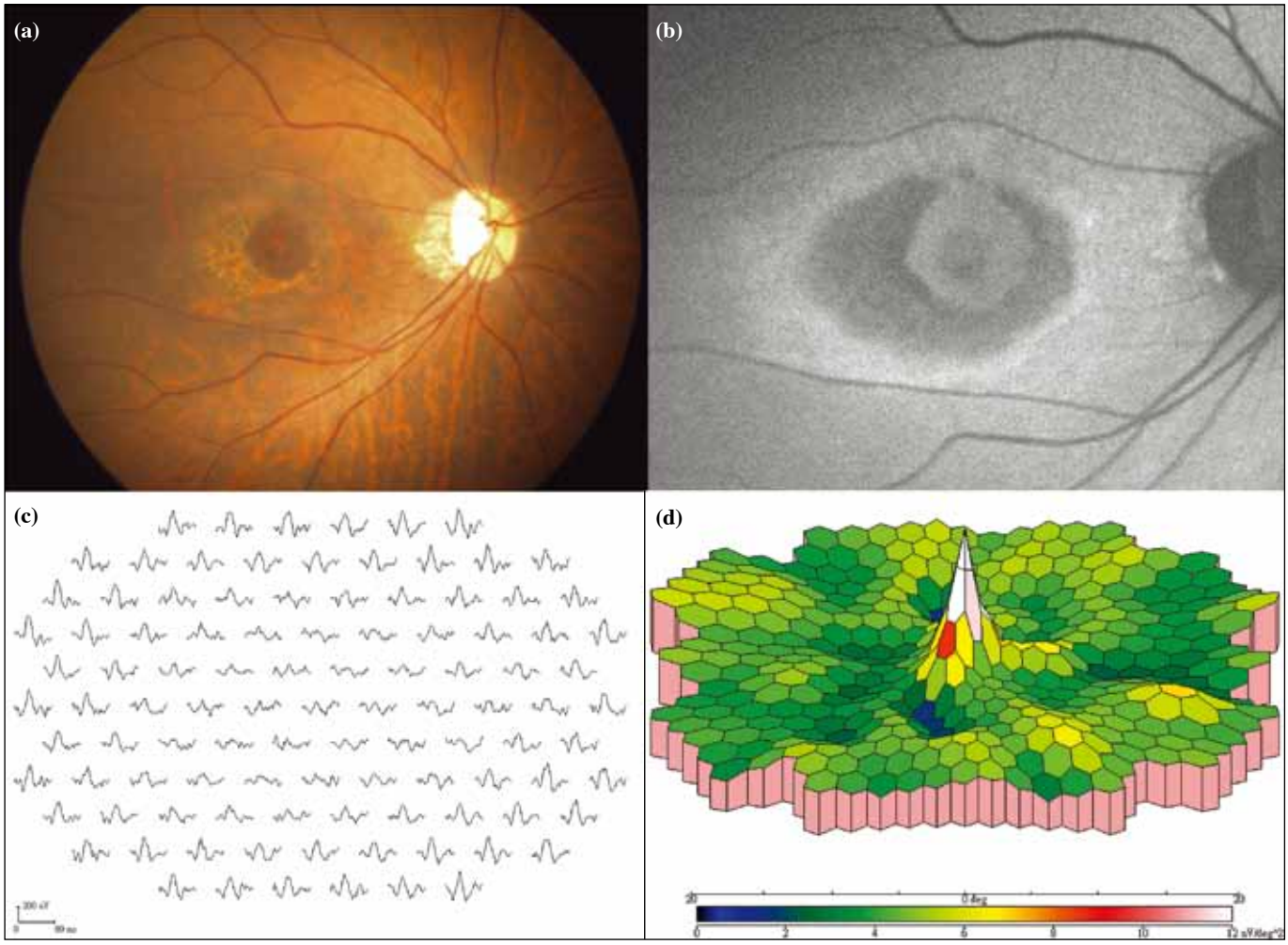

Figure 1. (a) Fundus photo of an eye with chloroquine toxicity showing the characteristic annular pigmentary changes at the macula. (b) Fundus autofluorescence showing reduced autofluorescence at the macula due to atrophy of the retinal pigment epithelial (RPE) cells with surrounding increased autofluorescence due to increased RPE cell metabolism. (c) Multifocal electroretinography trace array and (d) 3-dimensional response density plot showing paracentral reduction in response amplitude.

10-2 Humphrey visual field mean deviation value. Besides the visual field findings, studies have also demonstrated that mfERG correlated with anatomical findings in HCQ retinopathy. Fundus autofluorescence (FAF) is a method to image the macula, which detects early RPE alterations. Kellner et al[37] compared mfERG to FAF in the assessment of CQ or HCQ retinopathy. Among the 13 patients who had mfERG abnormalities, only 8 had abnormal FAF due to RPE alterations associated with CQ or HCQ toxicity, suggesting that the former has superior sensitivity. Rodriguez-Padilla et al[45] performed a cross-sectional study in 15 patients, with a view to compare mfERG to high-speed ultra-high resolution optical coherence tomography (OCT) imaging. mfERG abnormalities showed a good correlation with the perifoveal photoreceptor inner-outer segment junction disruption noted with OCT.

In recent years, a novel technique to analyze mfERG responses in HCQ toxicity has been evaluated by Lyons and Severns.[42,46] In their retrospective cross-sectional study,[46] 67 patients on HCQ had mfERG recordings; the ratios of the P1 amplitude of the central rings to the P1 amplitudes of the peripheral rings were calculated for analysis. The advantage of using ring ratios is that the intra- and inter-individual variations can be reduced. Moreover, the results demonstrated that while the P1 amplitude ring ratios might be affected by age, the 99% normal limits of the ring ratios were not influenced by age and thus the ratios can be evaluated without requiring age adjustment. This allowed comparison to be made even without age adjustment. In their study, 28% of the 131 eyes had abnormal ring ratios. The most frequently observed mfERG abnormalities were increased ring 1 to 2 and ring 1 to 3 ratios. These findings suggest pericentral retinal dysfunction conforming to HCQ toxicity, which mostly affects the perifoveal area.

The aforementioned studies have demonstrated that mfERG is very useful in the assessment of CQ and HCQ retinal toxicity, and allows early detection of retinal dysfunction before other clinical parameters became normal. Moreover, it allows the monitoring of the potential retinal functional recovery after drug withdrawal. mfERG has thus been incorporated in the latest American Academy of Ophthalmology recommendations for CQ and HCQ toxicity

screening.[47]

Quinine

Quinine is an anti-malarial drug and is also used to treat nocturnal leg cramps in an off-label manner. Verdon[48] reported a case of ocular toxicity after an overdose of quinine because of attempted suicide. The patient was assessed 9 months after the event. Her visual fields were constricted and OCT showed thinning of the middle and inner retina. mfERG showed reduction in responses at all locations, which became more marked in the periphery and the waveforms became electronegative beyond 6 degrees of fixation. This contrasts with other anti-malarial drug toxicities such as HCQ in which the reduction in mfERG responses is more prominent over the pericentral region.

Vigabatrin

Vigabatrin is an irreversible inhibitor of gamma-aminobutyric acid transaminase used in the treatment of epilepsy. One of its side-effects is visual field constriction. Electrophysiological studies have suggested this might be due to toxic effects of vigabatrin on the retina. Since the visual field constrictions are often localized binasally, mfERG has been used to evaluate the retinal dysfunction topographically in patients taking this drug.[49-55] Using mfERG, it was demonstrated that patients with visual field defects attributed to vigabatrin had reduced generalized or peripheral response amplitudes. In some patients, the abnormalities in mfERG response amplitudes appeared to correlate well with their visual field defects.[50,54] However, the abnormalities may also be more diffuse than the visual field findings.[50,52] Besch et al[49] carried out further investigations on the multifocal oscillatory potentials and second-order mfERG responses in patients on vigabatrin who had visual field defects. These patients had delayed multifocal oscillatory potentials and in cases with severe visual field defects, there were also delays in second-order mfERG implicit times. These findings indicate that vigabatrin-related visual field defects may be a result of inner retinal dysfunction of retinal ganglion cells.

Amiodarone

Amiodarone is used in the treatment of cardiac tachyarrhythmias. Long-term use of amiodarone has been associated with full-field and pattern ERG abnormalities. Shaikh et al[56] performed mfERG studies in patients who had been on long-term amiodarone therapy to evaluate possible retinal toxicity topographically. Some patients had subnormal P1 amplitudes and mild prolongation in P1 implicit times. The authors believed that the mfERG changes were probably age-related or due to testing variability, and further studies were needed to determine the extent of retinal toxicity associated with long-term therapy.

Sildenafil

Sildenafil is used in the treatment of erectile dysfunction and one of its reported side-effects is color vision disturbance. mfERG has been used to evaluate the acute effects of sildenafil on central retinal function in 14 healthy volunteers given sildenafil.[57] One hour after the intake, there were slight but significant reductions in P1 amplitudes and delays in P1 implicit times at all retinal eccentricities. The mfERG changes were the largest in the central macula with about 20% reduction in P1 amplitude and 5 to 9% increase in P1 implicit times. In some patients, the mfERG changes persisted for up to 5 hours and provided objective evidence that sildenafil may result in acute retinal dysfunction that could account for the transient visual disturbances some patients experience. Since sildenafil has now been approved for long-term use in patients with pulmonary arterial hypertension, Zoumalan et al[58] studied the mfERG changes in the latter patients. Three patients who had taken sildenafil for 1 to 4 years were asked to withhold their regular dose for 9 to 12 hours. mfERG was performed at baseline, after withholding the drug for 9 to 12 hours, and 1 hour after resuming the drug. At baseline, the mfERG amplitudes were within the normal range but the implicit times were increased in 3 out of the 4 subjects. When sildenafil was withheld, mfERG responses showed mild increases in amplitude and shortening in implicit times. They returned to baseline 1 hour after resuming the drug. The authors concluded that the chronic use of sildenafil is probably not seriously toxic to the retina.

Desferioxamine

Desferioxamine is a chelating agent used to treat iron overload in patients receiving long-term blood transfusion and its use may be associated with toxic retinopathy. Schmidt and Finke[59] documented reduction in mfERG amplitude in the central retina in a patient who developed bull's eye maculopathy after such therapy. Kertes et al[60] showed that there were bilateral reductions in response densities at the central retina, which corresponded with the pigmentary changes observed with desferrioxamine toxicity. After cessation of the treatment, the decline in retinal function stabilized as reflected by mfERG. Serial mfERG recordings allowed objective quantification and monitoring of retinal toxicity caused by deferoxamine.

Ethambutol

Ethambutol is an anti-tuberculosis drug that may cause optic neuropathy; such toxicity has been demonstrated at the retinal level and macula using mfERG.[61-64] Lai et al[61] reported a generalized reduction in central mfERG responses in a patient with ethambutol-induced optic neuropathy. The area of abnormality was more extensive than the central scotoma detected by automated perimetry, indicating diffuse impairment in macular function. After cessation of ethambutol, increase in mfERG response paralleled with the improvement in visual acuity. Behbehani et al[62] also reported mfERG response abnormalities in 4 patients with ethambutol-associated visual loss. Two of the patients had no visible optic nerve or fundal abnormalities. Analysis showed that the patients had significant reductions in N1 response amplitude compared to controls. Liu et al[63] reported 2 cases of bitemporal visual defects after taking ethambutol. The area of reductions in mfERG response amplitudes

corresponded to the visual field detects. A cross-sectional observational study comparing 17 asymptomatic patients on ethambutol with controls by Lai et al,[64] demonstrated significantly more delayed mfERG P1 implicit times of rings 4-6 in the ethambutol group than in the controls. Based on these studies, mfERG may be a useful tool in the diagnosis and serial assessment of ethambutol-related retinal toxicity. Some of the findings, however, might also be related to eccentric fixation caused by ethambutol-induced optic neuropathy and therefore result in reduced retinal response amplitudes.

Nefazodone

Nefazodone is an anti-depressant, which blocks postsynaptic serotonin type-2 (5HT2) receptors and its use has been associated with blurred vision and visual disturbances. Luu et al[65] reported the use of mfERG to evaluate retinal dysfunction 3 years after a patient developed severe bilateral visual loss after an 8-week course of nefazodone therapy. No abnormality was detected using conventional full-field ERG. Severe depression in mfERG responses over the central retina with sparing of the nasal retinal responses was documented, suggesting that the drug may cause retinal toxicity at the central macula.

Thallium

Thallium is used as a radiotracer in cardiac stress tests. Thallium poisoning may cause visual impairment due to optic atrophy. mfERG has been applied to assess the retinal toxicity in a patient with chronic thallium poisoning, in which the full-field ERG was normal.[66] The poisoning led to a reduction in central mfERG response amplitude with preservation of the responses from the mid-peripheral retina. This result suggests that, in addition to optic neuropathy, thallium can result in central retinal toxicity. However, eccentric fixation caused by the optic neuropathy might also have accounted for some of the mfERG abnormalities.

Alpha-interferon

The combination of antiviral drugs like ribavirin with alpha-interferon therapy have been used in the treatment of chronic hepatitis C. An ocular side-effect of alpha-interferon therapy is retinal ischemia, and mfERG has been used to assess the associated retinal dysfunction. Chisholm et al[67] performed mfERG in 10 patients receiving sustained release pegylated alpha-2a interferon therapy. mfERG showed that 5 of them developed reductions in retinal responses compared to baseline recordings. Some of the mfERG abnormalities were found in clinically asymptomatic patients, with normal fundal appearances. mfERG provided objective evidence that patients may develop retinal dysfunction following alpha-interferon therapy, and this technique may also be useful in monitoring retinal function in patients receiving this drug.

Tamoxifen

Tamoxifen, which is used in the treatment of breast cancer, is known to be potentially toxic to the cornea, lens, retina and the optic nerve. In a study by Ritter et al,[68] mfERG recordings were obtained from 7 patients taking tamoxifen who complained of visual disturbance. One patient had crystalline deposits in the cornea and macula, but in the others clinical examination revealed no abnormality. Five of the patients had abnormal mfERG responses. Thus, the authors recommended using mfERG to detect tamoxifen toxicity in symptomatic patients who do not have characteristic clinical signs. However, in another study by Salomäo et al,[69] mfERG response amplitudes and implicit times were found to be no different in breast cancer patients taking tamoxifen, breast cancer patients not taking tamoxifen, and normal controls. These researchers also performed serial mfERG recordings on 3 patients taking tamoxifen over the course of as long as 25 months. All patients, including one who developed retinal crystals, had normal mfERG responses over that period of time. The authors concluded that mfERG might not be sensitive enough to detect tamoxifen-related retinal toxicity. Further studies are therefore needed to delineate the role of mfERG in the detection of tamoxifen-related retinal toxicity.

Calcium formate

Calcium formate is a dietary calcium supplement used for the prevention of osteoporosis. High concentrations in the serum are reported to be toxic to the retina and optic nerve. A prospective study by Altaweel et al[70] studied the changes in mfERG responses before and after a course of calcium formate in 12 adult females. All subjects took 1300 mg 3 times a day for 14 days. mfERG performed at baseline and at day 15 showed no significant change in the response amplitudes and latencies in all 6 rings. However, the follow-up period was relatively short, and might not have excluded toxicity to the retina in the long term.

Future development of multifocal electroretinography techniques in assessing retinal dysfunction caused by pharmacological agents

Although the above-mentioned studies have shown mfERG to be a useful investigation tool in assessing functional abnormalities of the macula caused by various pharmacological agents, it has been suggested that in its standard form it still lacks sufficient sensitivity to detect some functional abnormalities. Modifications of the technique have been attempted to further optimize the ability of mfERG for this purpose. Examples of these modifications include changing the parameters of the stimulus and the use of wide-field mfERG (WF-mfERG).

Alterations in the multifocal electroretinography stimulus parameters

By altering the mfERG stimulus parameters, researchers can use it to investigate various aspects of retinal electrophysiology at different retinal topographic locations. The use of 8 bright frames followed by 8 dark frames allowed the measurement of multifocal on-and-off responses.[71,72] Multifocal oscillatory potentials can also be

measured by using the slow-flash mfERG with insertion of 3 dark frames between the multifocal stimuli.[73,74] Responses from ganglion cells and the optic nerve head can also be enhanced by using alternating dark and global flashes between the multifocal stimuli.[75,76] This technique has been utilized to assess HCQ toxicity[35] and further research to assess its utility is warranted.

Another modification of the mfERG stimulus parameter is to select the most appropriate emission spectrum of the color stimulus, so that specific mfERG responses from L- and M-cones can be recorded topographically.[77-79] This technique of silent substitution can differentiate protanopes and deuteranopes from trichromat individuals, and has helped in the understanding of different cone electrophysiological activities.[77,79] Apart from using mfERG for recording responses from the cone system, rod-mediated mfERG can also be recorded through dark-adaptation and insertion of dark frames between the multifocal flashes in order to study the topographical function of the rod system.[80-84] Since retinal toxicity caused by a particular pharmacological agent might be specific to a particular retinal cell type, these cone and rod-isolating techniques will enable more detailed electrophysiological assessment of specific retinal cell dysfunction caused by the pharmacological agents topographically.

Wide-field multifocal electroretinography

The WF-mfERG was developed recently and has the potential to stimulate more peripheral retinal areas compared to conventional mfERG (**Figure 2**). While the testing field of conventional mfERG is around 50-60°, up to 90° of retina can be stimulated using WF-mfERG. Studies have demonstrated that it is useful in assessing peripheral retinal dysfunction in patients with central retinal vein occlusion and retinitis pigmentosa.[85,86]

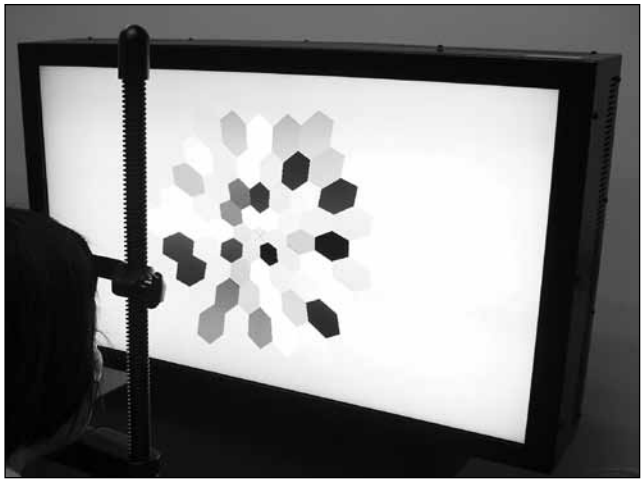

Figure 2. Widescreen liquid crystal display used for wide-field multifocal electroretinography.

One application of the WF-mfERG is the evaluation of retinal dysfunction caused by pharmacological agents such as vigabatrin toxicity.[87-89] Since conventional mfERG can only record the responses from the central 50-60° of the retina and not the periphery, peripheral visual field constriction as caused by vigabatrin therapy could be more readily assessed. McDonagh et al[88] conducted such a study in patients taking vigabatrin. Among all the WF-mfERG parameters, the most consistent overall predictor of bilateral visual field defects was the difference between the central and peripheral implicit times. Using this parameter, it was shown that WF-mfERG had 100% sensitivity and 86% specificity for objectively detecting vigabatrin-induced visual field defects. Gonzalez et al[89] studied the visual fields and WF-mfERG recordings of patients with epilepsy with and without exposure to vigabatrin. They noted visual field defects even in patients never exposed to the drug, whereas WF-mfERG abnormalities were only detected in patients with exposure to vigabatrin. This suggests that WF-mfERG might be more specific than visual field evaluation in detecting vigabatrin toxicity. Since the WF-mfERG system is currently being introduced commercially, its increasing availability should broaden the ability of ophthalmologists to assess retinal dysfunction.

Conclusion

It is evident that mfERG is a useful investigation tool for evaluating retinal dysfunction caused by various ocular or systemic pharmacological agents. It has enhanced understanding of the underlying pathophysiology of retinal dysfunction due to therapeutic agents. It can also provide valuable options for the objective assessment of toxic retinopathy and enable safer administration of treatment. This is particularly important, since various new treatment modalities for macular diseases such as dry and neovascular AMD are being introduced for clinical use. In which case, mfERG can provide an objective outcome measures to assess their efficacy and adverse effects. Further new developments and refinements of the technique will broaden the ability of mfERG to detect retinal dysfunction associated with pharmacological therapy in the future.

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Corrigendum

"Intraocular gas in vitreoretinal surgery" (July 2010;14:8-13). On page 10, second paragraph under the heading "Pneumatic retinopexy in retinal detachment", the first sentence should have read "The technique involves the injection of intraocular gas before or after retinopexy, application of cryotherapy or laser around the retinal breaks, and maintenance of specific head postures after surgery." rather than "The technique involves the injection of intraocular gas before or after retinopexy, which creates retinal breaks with cryotherapy or laser, and maintenance of specific head postures after surgery." as printed.