Retinal Toxicity of Indocyanine Green in Albino Rabbits

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PURPOSE. Intravitreal indocyanine green (ICG) is commonly used in vitreoretinal surgery. The purpose of this study was to evaluate possible toxicity of ICG in the retina of albino rabbits.

METHODS. Twenty-two albino rabbits were injected intravitreally with 0.1 mL ICG solution in one eye, and three rabbits were studied for the effects of 0.1 mL distilled water. All rabbits were injected intravitreally with 0.1 mL saline into the fellow eye, which served as the control. The electroretinogram (ERG) and visual evoked potential (VEP) were recorded from each rabbit at different time intervals after injection. The rabbits were killed at the termination of the follow-up periods and their retinas prepared for histologic examination at the light microscopic level.

RESULTS. Three hours after injection, the ERG responses were reduced in amplitude in all ICG-injected eyes, and the VEPs were of abnormal pattern (reduced amplitude and delayed). Partial dose-dependent recovery was observed during 4 weeks of follow-up. Light microscopy of the retinas of the experimental eyes exhibited considerable damage to all retinal layers in all eyes studied that received the highest ICG dose.

CONCLUSIONS. ICG is potentially toxic to all retinal layers of the albino rabbit. Although it is difficult to extrapolate these findings directly to human eyes, caution should be exercised when using ICG intravitreally. (Invest Ophthalmol Vis Sci. 2006;47: 2100–2107) DOI:10.1167/iovs.05-0206

Intravenous administration of indocyanine green (ICG) is commonly used in the ophthalmic clinic for detecting disease in the choroidal vasculature.1–3 In the past few years, intravitreal administration of ICG during vitrectomy has been suggested for idiopathic macular hole or for retinal detachment secondary to myopic macular hole.4–11 The dye selectively stains the internal limiting membrane (ILM),5,7 improving visualization and facilitating removal of the ILM without injuring the underlying unstained retina.

Despite the surgical benefits of ICG staining and the successful anatomic results of its use, recent reports have demonstrated unsatisfactory functional outcome. Visual acuity was poorer in eyes treated with ICG compared with those of control subjects,12–14 and visual field defects were found after surgery in eyes that had undergone ICG-assisted peeling of the ILM during vitrectomy surgery.15,16 Twelve months of follow-up that included electroretinography (ERG), optical coherence tomography (OCT), and fluorescein angiography measurements of patients who underwent ILM peeling with ICG validated the presence of ICG-associated damage to ganglion cells and their axons in addition to retinal pigment epithelial (RPE) damage.16 Funduscopic findings in eyes after ILM peeling during macular hole surgery revealed unusual RPE atrophy in areas where the cells were in direct contact with ICG.17 These and other studies18,19 raised the possibility that ICG is toxic to the retina, and prompted toxicity studies in human cadaveric eyes and animal models.

Histologic examination of retinas of eyes undergoing ICG-assisted removal of ILM have demonstrated cleavage planes within the innermost retinal layers.20 Experimental macular surgery using ICG in donor eyes has shown that ICG alone causes rupture of Müller cells with detachment of the ILM. This ICG-induced damage is exacerbated if the retina is exposed to light containing wavelengths longer than 620 nm.21 Several studies have demonstrated ICG toxicity to human RPE cells in vitro that could cause cell-cycle arrest and apoptosis in the presence of acute illumination.22,23 Toxicity studies in animal models have indicated ICG toxicity in different retinal structures. Whereas one study in a porcine model of eyes that had been obtained 5 hours after enucleation and exposed to different concentrations of ICG showed no histologic damage,24 another study showed ICG-induced RPE atrophy in a porcine model of retinal hole.25 ICG-injected subretinally in rabbits resulted in severe, dose-dependent morphologic damage to the outer retina and photoreceptors.26,27 In two studies involving electroretinogram (ERG) recording to test retinal function, ICG injected intravitreally led to permanent reduction in retinal function.28,29 ICG has been found to induce functional damage in the rat retina without any apparent morphologic damage, even with a low dose of the dye (0.025 mg/mL).30 Finally, ICG toxicity to rat ganglion cells has been documented in vitro and in vivo.31 This observation is of extreme importance, since, in ophthalmic surgery, ICG is applied to the surface of the retina from the vitreal side, and the first cells to have direct contact with the drug are the retinal ganglion cells.

The purpose of the present study was to evaluate possible toxicity of different concentrations of intravitreally injected ICG in a rabbit model. To test possible ICG toxicity to the ganglion cells and to distal retinal layers, we recorded respectively the visual-evoked potentials (VEPs) and the electroretinogram (ERG).

METHODS

Animals

Twenty-five adult albino rabbits weighing 2.5 to 3.0 kg each were included in the study. The rabbits were housed in a 12-hour light–dark cycle and were allowed free access to water and food. All the experimental procedures adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and to institutional guidelines.

Before intravitreal injection and electrophysiologic recordings, the rabbits were anesthetized by an intramuscular injection (0.5 mL/kg body weight) of a mixture containing ketamine hydrochloride (10 mg/mL), acepromazine maleate solution (10%), and xylazine solution (2%) at a ratio of 1:0.2:0.3. Topical anesthesia (benoxinate HCl 0.4%) was administered to reduce the animal’s discomfort. The pupils were fully dilated with cyclopentolate hydrochloride 1%.

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Intravitreal Injection

Each rabbit was injected intravitreally in both eyes as described before.31 One eye, usually the right one, was injected with the experimental solution (ICG or distilled water) and the other with saline (control). A 25-gauge needle attached to a 1.0-mL tuberculin syringe was inserted into the vitreous approximately 1 mm posterior to the limbus. The syringe was directed under visual control with an indirect ophthalmoscope (Neitz Instruments, Tokyo, Japan) toward the center of the vitreous above the optic disc. A volume of 0.1 mL was then slowly injected.

Electroretinogram

Flash ERG responses were recorded31 from the experimental and control eyes, by using corneal electrodes (Medical Workshop, Groningen, The Netherlands). The reference and ground electrodes were made of stainless-steel surgical needles and were inserted into the ears. The ERG signals were amplified (×20,000) and filtered (0.3–300 Hz) by differential amplifiers (Grass-Telefactor, West Warwick, RI). Light stimuli were obtained from a Ganzfeld light source (LKC Technologies, Gaithersburg, MD) with a maximum intensity of 5.76 cd·s/m².

The ERG responses were recorded in the dark-adapted state (at least 3 hours in darkness) and then in the light-adapted state (background illumination of 1.15 cd/m²). Six responses elicited by identical flashes applied at 10-second intervals were averaged in the dark-adapted state, and 15 responses elicited at a frequency of 1 Hz were averaged in the light-adapted state.

ERG analysis was based on measurements of the b-wave amplitude from the trough of the a-wave to the peak of the b-wave. The b-waves of the experimental and control eyes were plotted as a function of log flash intensity for each rabbit. The response-intensity curve of the ERG b-wave was fitted to a Michaelis-Menten–type hyperbolic function32

\[
\frac{V}{V_{\text{max}}} = \frac{1}{1 + \sigma}
\]

where \(V\) is the amplitude of the ERG b-wave elicited by a stimulus of intensity \(I\), \(V_{\text{max}}\) is the maximum response amplitude, and \(\sigma\) is the semisaturation constant. Functional damage in the experimental eye was assessed from the \(V_{\text{max}}\) ratio (experimental/control), and the difference in log \(\sigma\) (experimental – control).31 With this approach, technical factors, such as depth of anesthesia and duration of darkadaptation did not affect the assessment of ICG-induced damage.

Visual-Evoked Potentials

The VEPs were recorded with a stainless-steel needle acting as the active electrode that was inserted under the skin above the area of the visual cortex, midway between the two ears. The reference and ground electrodes were inserted in the ears. The signal was amplified (×500,000) and filtered (1–100 Hz) by a differential amplifier (Grass-Telefactor). With this electrode configuration, monocular light stimuli yielded very similar VEPs in nontreated animals. Fifty stimuli were delivered at a rate of 1.1 Hz, and the resultant signals were digitized and averaged by the computer. To minimize possible contamination of the VEPs due to light absorbed by the ICG dye, we elicited the VEPs with the brightest light stimuli 5.76 cd·s/m² available in our photostimulator (PS22; Grass-Telefactor).

The VEP responses were assessed quantitatively from their temporal pattern and amplitudes. The most easily identifiable waves of the flash VEP in rabbits were an initial negative wave that was followed by a prominent positive wave. The VEP amplitude was measured from the trough of the first negative wave to the peak of the following positive wave. Temporal properties of the VEP were defined by the time interval from stimulus onset to the trough of the first negative wave, termed the implicit time.

Indocyanine Green

ICG was prepared according to the manufacturer’s instructions (Akron, Buffalo Grove, IL) by dissolving 25 mg powder in 10 mL distilled water. The osmolarity of the solution was 7 mOsm. The rabbits were divided into four groups according to the injected solution. The first group (n = 9) was injected with 0.1 mL ICG solution, having a concentration of 2.5 mg/mL (original vial concentration). Rabbits in the second group (n = 6) were tested for the effects of 1.25 mg/mL ICG solution (0.1 mL), and those in the third group (n = 7) with a concentration of 0.5 mg/mL (0.1 mL). The fourth group (n = 5) served as a control for the effects of osmolarity on retinal function. The rabbits belonging to this group were injected with 0.1 mL distilled water in one eye. All 25 rabbits were injected intravitreally with 0.1 mL saline into the left eye, which served as control.
Statistical Analysis

The ERG parameters ($V_{max}$ and $\sigma$) and the VEP parameters (amplitude and implicit time) were first tested for dependency of variance on the mean by using the Levene test for homogeneity of variance. Then, the parameters were tested for statistical significance by using the mixed model of analysis of variance with repeated measures that could be used for incomplete data points.

Histologic Examination

Histologic observations seeking abnormal retinal structures were conducted at the light microscopic level. The enucleated eye was soaked for 10 minutes in 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M of phosphate buffer (pH 7.4). The eyeball was opened 2 mm posterior to the limbus (pars plana) and fixed for 72 hours. After the lens and the vitreous were removed, the posterior eye cup was bi-

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**Figure 2.** ERG follow-up of one albino rabbit that was injected with the highest ICG dose (0.25 mg). Dark-adapted ERG responses were elicited by light stimuli of different intensities as denoted in log units of cd-s/m<sup>2</sup> to the left of each row of responses. ERG responses were recorded 3 hours, 1 week, and 4 weeks after ICG injection. Each pair of responses compares the ERG of the experimental eye to that of the control eye (bottom and top traces, respectively). Arrow: timing of the light stimulus.

**Figure 3.** Response–intensity data for the dark-adapted ERG b-wave were measured in same rabbit as shown in Figure 2. ERG data of the experimental and control eyes are compared (filled and open symbols, respectively). The data were fitted to a Michaelis-Menten hyperbolic relationship (see the equation; dotted curve for the control eye and a continuous curve for the experimental eye).
Table 1. Maximum b-Wave Amplitude (Vmax) and Semi-Saturation Constant (σ)

<table>
<thead>
<tr>
<th></th>
<th>Vmax (exp)</th>
<th>Vmax (control)</th>
<th>Vmax ratio</th>
<th>Log σ (exp)</th>
<th>Log σ (control)</th>
<th>ΔLog σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Hours</td>
<td>104</td>
<td>228</td>
<td>0.46</td>
<td>−1.53</td>
<td>−1.45</td>
<td>−0.08</td>
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<tr>
<td>1 Week</td>
<td>84</td>
<td>196</td>
<td>0.43</td>
<td>−1.58</td>
<td>−1.55</td>
<td>−0.03</td>
</tr>
<tr>
<td>4 Weeks</td>
<td>134</td>
<td>252</td>
<td>0.53</td>
<td>−1.72</td>
<td>−1.84</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Data are from the rabbit for which the electroretinogram responses and response-intensity data are shown in Figures 2 and 3, respectively. Indocyanine green toxicity was calculated from the Vmax ratio and the difference in log σ. Vmax is expressed in microvolts and σ in cd·s/m².

RESULTS

Clinical Observation

After intravitreal injection, ICG appeared as a floating green mass in the vitreous (Fig. 1A), whereas the eye injected with saline (Fig. 1B) appeared clear. During the follow-up period, pigmented particles were observed floating in the vitreous and on the retinal surface of the ICG-injected eye for 4 to 6 weeks, until they completely disappeared. Fundus examination performed 4 weeks after injection, detected no apparent changes.

Electroretinogram

Figure 2 shows representative ERG responses of one rabbit that were recorded at three time intervals (3 hours, 1 week, and 4 weeks) after intravitreal injection of 0.1 mL of the original 2.5 mg/mL vial solution (making an injected ICG dose of 0.25 mg). Dark-adapted ERG responses that were elicited by flashes of different intensities (denoted in log units to the left of each row) are shown for each recording session. The ERG of the experimental eye (bottom trace) is compared to the ERG of the control eye (top trace) in each pair of responses. The ERG responses in the experimental eye were reduced by approximately 50%, compared with the control eye when measured 3 hours after injection. The ERG responses of the rabbit in Figure 2 did not change appreciably during the 4-week follow-up period.

The pattern of the ICG effect and its dependency on time after injection are better illustrated by analyzing the response-intensity relationships. Figure 3 shows the response-intensity relationships for the dark-adapted b-waves of the experimental and control eyes of the same rabbit for which ERG responses are shown in Figure 2. The response-intensity data were fitted to the Michaelis-Menten hyperbolic function (see the equation) to derive the maximum b-wave amplitude (Vmax) and semisaturation constant (σ), summarized in Table 1. To assess the effects of ICG on the functional integrity of the experimental eye, we calculated the Vmax ratio (experimental eye/control eye) and the difference in the log σ. These values indicated a reduction of ~50% in Vmax throughout the 4 weeks of follow-up and a very small change in the semisaturation constant.

ERG recordings were conducted in all 22 rabbits at each period of follow-up (3 hours, 1 week and 4 weeks after injection). We derived the response-intensity curve and calculated the Vmax ratio and the log σ difference as discussed earlier. Figure 4 summarizes the Vmax ratio (mean ± SD) of the three groups of rabbits at each postinjection time. Follow-up lasted for 6 weeks in some rabbits, but their data were combined with those obtained at 4 weeks, since there were no major changes in the ERG responses past 4 weeks after ICG injection.

There was a reduction of Vmax ratio in all three groups of rabbits by 3 hours after injection. Partial recovery of the ERG responses was observed during 4 weeks of ERG follow-up. The extent of recovery depended on the injected dose. At 1-week after injection, there was no detectable change in the Vmax ratio in the rabbits injected with a dose of 0.25 mg, but improvement was demonstrated in the other two groups (injected with 0.125 and 0.05 mg). At the end of the follow-up period (4–6 weeks), the group treated with the lowest dose (0.05 mg) of ICG exhibited close to complete ERG recovery. The other two groups also showed recovery in their ERG recordings, but did not return to control levels.

Statistical analysis showed no interaction between time and treatment, between dose and treatment and between time and dose. Therefore, we were able to apply the statistical test to each dose group of rabbits separately. There was no significant

![Figure 4](image-url)
interaction between treatment and time for any of the ERG parameters. We found significant reduction in the maximum response amplitude \( (V_{\text{max}}) \) for the highest tested dose \( (P = 0.0004) \) and for the medium dose \( (P = 0.0202) \), but not for the lowest dose. The effects of ICG on the semisaturation constants of the b-wave response-intensity curves (Fig. 4B) were negligible in all three groups of rabbits, throughout the entire follow-up period.

Three rabbits that were tested for the effects of distilled water exhibited no ERG deficit throughout the entire period of follow-up (4 weeks). Mean \( V_{\text{max}} \) ratio and mean difference in \( \log \sigma \) are listed in Table 2.

### Visual-Evoked Potentials

Because ICG penetrated the retina from the vitreal side, the first cells to be exposed to it were the ganglion cells. We recorded the VEPs to test possible ICG toxicity to the ganglion cells and/or to the nerve fiber layer.

Figure 5 shows VEP responses elicited by monocular stimulation of the control and experimental eyes (top and bottom traces, respectively) of one rabbit that were recorded at 3 hours, 1 and 4 weeks after intravitreal injection of 0.25 mg ICG. The typical pattern of a negative wave appearing 40 to 60 ms after the light stimulus, followed by a positive wave, was seen in all recordings. However, the implicit time of the first negative wave is prolonged, and the amplitude of the positive wave of the VEP responses of the control eye remained substantially lower than that in the control eye during the entire follow-up period, whereas the implicit time recovered toward that of the control eye after 4 weeks. Statistical analysis revealed nonsignificant interaction between treatment and time for all three dose-groups for either of the VEP parameters. The VEP amplitude was significantly reduced in the treated eye compared with the control eye for all doses throughout the follow-up period \( (P = 0.0003, 0.0202, 0.0144 \text{ for the highest, medium, and lowest doses, respectively}) \). Significant prolongation of the implicit time for all periods of follow-up was found for the highest \( (P = 0.0039) \) and medium \( (P = 0.0222) \) doses, but not for the lowest dose.

### Histologic Findings

Histologic findings of retinas from two representative rabbits that were injected with the original vial concentration of ICG, receiving the highest \( 0.25 \text{ mg} \) or the lowest \( 0.05 \text{ mg} \) doses are demonstrated in Figure 7. All four micrographs were taken close to the site of injection. The retina of the experimental eye of the rabbit treated with the highest ICG dose (bottom left) exhibited considerable damage to all retinal layers, when compared with the control retina (bottom right). The outer nuclear layer (ONL) was very thin and contained only two rows of nuclei. The inner nuclear layer (INL) was also thinner than in the control retina and only a few ganglion cells were identifiable (bottom row). The retinas from the experimental and control eyes of the rabbit injected with the lowest dose of ICG \( 0.05 \text{ mg} \), appeared similar under the light microscope, suggesting no apparent damage to retinal morphology.
DISCUSSION

The electrophysiological and histologic findings in our study demonstrated dose-dependent functional and structural damage to the retina of albino rabbits by intravitreal injection of ICG. ICG exerted toxic effects on all retinal structures. The affected ERG responses indicated damage to the distal retina, and the abnormal VEPs were suggestive of damage to the proximal retina. Functional damage by ICG was evident early after injection (3 hours). The ERG responses were reduced in amplitude (Figs. 2, 3, 4), and the VEP responses were of subnormal amplitude and prolonged implicit time (Figs. 5, 6). Some of the effects of ICG were transient, with recovery being apparent within 4 weeks of follow-up, but permanent retinal damage developed with the highest two doses of ICG.

Immediately after injection, ICG appeared as a green mass floating in the vitreous (Fig. 1A). It absorbed some of the incident light, thus reducing the light intensity reaching the retina and causing the ERG responses to be reduced in amplitude. If the ICG had acted only as an optical filter, interposed in the light path, the response–intensity relationship of the ERG b-wave would be expected to be characterized by a normal maximum response \( V_{max} \) and an increased semisaturation constant \( \sigma \). This was not the case. In every rabbit, the \( V_{max} \) of the b-wave was reduced by ICG, whereas the semisaturation constant \( \sigma \) hardly changed (Fig. 4). Furthermore, we measured the transmittance of ICG solutions using all the concentrations that were studied. With the highest concentration (2.5 mg/mL), the transmittance between 450 to 600 nm was approximately 40% and lower at wavelengths shorter than 450 nm or longer than 600 nm, indicating only a small effect on the light impinging on the retina. This low effect is supported by the visibility of retinal blood vessels through the ICG dye in the vitreous. Thus, the early effects of ICG on the ERG responses probably reflected reduced retinal function and not optical interference. It should also be noted that a permanent ERG deficit was observed after 4-weeks of follow-up, when most of the ICG had cleared from the vitreous, supporting the notion of ICG-induced retinal damage.

The flash ERG reflects mainly light-induced activity in the distal retina, with minor contributions by light-induced activity in the proximal retina. Blocking activity in the proximal retina by specific antagonists leads to augmentation of the ERG. Therefore, damage to the proximal retina is expected to cause the ERG responses to increase in amplitude or at least not to
change. Because ICG caused ERG diminution, we conclude that ICG, diffusing through the retina from the vitreal side, can exert toxic actions on distal retinal neurons. ICG toxicity to the distal retina, including the RPE, has also been demonstrated by morphologic analysis of the rabbit retina after subretinal injection of ICG, as well as in a porcine model of retinal hole.

Findings in studies of donor human eyes and of human RPE cells in culture have suggested that ICG toxicity is intensified by illumination. In our experiments, however, the rabbits were exposed to bright light only during the intravitreal injection procedure, after which they were kept in darkness for 3 hours before the first-injection ERG recordings, which showed functional deficit (Fig. 4). Thus, photic damage can be excluded in the present study. Another mechanism of ICG toxicity was attributed to the hypo-osmolarity of the solvent.

This mechanism could not be involved in our model because a volume of 0.1 mL of ICG solution was injected into a vitreous of approximately 1.47 mL in volume (for rabbits weighing 1.8–2.7 kg), leading to only a minor change in vitreal osmolarity. Furthermore, in control experiments, we tested the effects of 0.1 mL distilled water on retinal function, and found no ERG deficit for as long as 4 weeks of follow-up (Table 2). Thus, it is likely that several pathways are involved in ICG-induced neuronal damage.

The effects of ICG on the VEP indicate reduced retinal output to the brain and subnormal conduction via the optic nerve. These findings could reflect ICG-induced damage to distal retinal neurons, to proximal retinal neurons, or to both. Because ICG was found to be toxic to rat retinal ganglion cells, we suggest that the drug is toxic to all retinal cells, leading to deterioration of the flash-elicited ERG and VEP responses.

The findings reported herein and by others indicate that intravitreal injection of ICG in rabbits or rats can cause permanent structural and functional damage to the retina. The relevance of these observations to the use of ICG in vitreoretinal surgery should be considered. In the animal studies, ICG was injected into the vitreous and cleared within 10 days in rats or within 4 to 6 weeks in rabbits. In clinical practice, ICG is applied to the ILM for 10 to 60 seconds and then washed away, followed by a full vitrectomy. Thus, the time of exposure to ICG differs between clinical use and animal experimentation. Several recent reports, however, have described long-lasting fluorescence of ICG emanating from the retina, even though it had been washed away. Giardella et al. reported four cases in which persistent ICG fluorescence in the central macula was detected up to 8 months after surgery. Ashikari et al. reported two cases in which examination with a scanning laser ophthalmoscope detected fluorescence from residual ICG up to 9 months after surgery, even though no ICG staining of the retina was visible on clinical examination. Tadayoni et al. reported 17 patients who underwent vitrectomy with the use of ICG and demonstrated persistent diffuse fluorescence of the fundus at 1 and 3 months after surgery, with only the optic disc remaining fluorescent at 6 months after surgery. Weinberger et al. reported one case in which persistent fluorescence was demonstrated 6 weeks after vitrectomy, but there was normal function with improved visual acuity and regular amplitudes on multifocal ERG. These reports demonstrate long-lasting contact between ICG and retinal elements after use of ICG in vitreoretinal surgery raising the possibility of ICG toxicity.

Our experimental approach did not mimic the clinical use of ICG. However, taking our data together with the many other reports on ICG toxicity in animal models, cadaveric human eyes, and cultured human retinal cells, ICG should be used in vitreoretinal surgery with caution. The concentration of the dye should be maintained at a minimal level that will still be beneficial for the surgeon. The time of exposure should be as short as possible, and washout should be meticulous to prevent long-standing exposure of the retina to ICG.

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