

Safety of intravitreal quinupristin/dalfopristin in an animal model

Veronica E. Giordano¹, Sergio E. Hernandez-Da Mota², Tania N. Adabache-Guel¹, Armando Castillejos-Chevez³, Sonia Corredor-Casas⁴, Samantha M. Salinas-Longoria¹, Rafael Romero-Vera¹, Juan M. Jimenez-Sierra¹, Jose L. Guerrero-Naranjo¹, Virgilio Morales-Canton¹

¹Department of Ophthalmology, Retina and Vitreous Service, Asociacion para Evitar la Ceguera en Mexico, Vicente García Torres 46, Coyoacán, Barrio San Lucas, Mexico City 04030, Mexico

²Ophthalmology Service, Clinica David, Boulevard García de León 598, Nueva Chapultepec, Morelia, Michoacán 58280, Mexico

³Department of Ophthalmology, Glaucoma Service, Asociacion para Evitar la Ceguera en Mexico, Vicente García Torres 46, Coyoacán, Barrio San Lucas, Mexico City 04030, Mexico

⁴Department of Ophthalmology, Pathology Service, Asociacion para Evitar la Ceguera en Mexico, Vicente García Torres 46, Coyoacán, Barrio San Lucas, Mexico City 04030, Mexico

Correspondence to: Veronica E. Giordano. Division del Norte 2743 A 303, San Lucas 04030, Coyoacán, Distrito Federal, Mexico. pinigiordano@hotmail.com

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Abstract

• **AIM:** To determine whether different intravitreal doses of quinupristin/dalfopristin lead to electroretinographic or histological changes in the rabbit retina over one month period after injection.

• **METHODS:** Eighteen New Zealand white rabbits were divided into three treatment groups (groups 1 to 3) and different intravitreal doses of quinupristin/dalfopristin were tested in each group. The right eye was injected with the drug and the left eye received intravitreal injection of 5% dextrose water and served as control eye. The doses delivered to each group were 0.1 mg/0.1 mL, 1 mg/0.1 mL and 10 mg/0.1 mL. Simultaneous, bilateral, dark-adapted electroretinography and clinical images of both eyes were obtained in all groups before injection (baseline) and after 7, 14, 21 and 28d, followed by enucleation for histological examination.

• **RESULTS:** Subjects in the group 1 showed no signs of toxicity in the electroretinogram when compared with groups 2 and 3 (Kruskall-Wallis test, $P=0.000$). By day 7, no electrical response to light stimuli was recorded in the treated eyes in groups 2 and 3, consistent with severe damage due to retinal toxicity. Light microscopy revealed

no significant histopathological changes in the group 1, while rabbits in groups 2 and 3 had signs of granulomatous inflammation in most cases.

• **CONCLUSION:** Intravitreal 0.1 mg/0.1 mL doses of quinupristin/dalfopristin do not lead to electroretinographic or histological signs of retinal toxicity compared with 1 mg/0.1 mL and 10 mg/0.1 mL in this rabbit model.

• **KEYWORDS:** endophthalmitis; quinupristin/dalfopristin; retinal toxicity

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INTRODUCTION

Acute endophthalmitis is one of the most challenging complications in ophthalmic surgery and portends a poor visual outcome. Because of the difficulty in obtaining effective antibiotic levels within the eye *via* parenteral or oral drug administration, intravitreal injection still remains the mainstay of therapy. Because of the current high prevalence of infections caused by *Staphylococcus sp.*, the treatment of choice is vancomycin and ceftazidime in order to cover Gram-negative bacteria; these are administered with or without steroids^[1]. However, in many cases, this treatment is no longer effective particularly as a result of the increasing prevalence of resistant bacteria found in clinical practice.

Quinupristin/Dalfopristin (Q-D) (Synecid, DSM Pharmaceuticals, Inc., Greenville, NC, USA) is a novel drug that combines two streptogramins: quinupristin (a B streptogramin) and dalfopristin (an A streptogramin) in a 30:70 ratio; it is indicated in the treatment of serious infections caused by multiresistant Gram-positive organisms and exhibits extended activity against vancomycin-resistant strains of staphylococci^[2-4].

Q-D has a minimum inhibitory concentration (MIC) $\leq 1 \mu\text{g/mL}$ in 90% of Gram-positive isolates resistant to other drugs, including *Staphylococcus aureus* and *Enterococcus faecium* and a prolonged antibiotic effect (up to 10h)^[2-4]. Q-D has also demonstrated *in vitro* inhibitory

activity of proinflammatory mediators, thus possibly affecting immunomodulatory activity^[5].

There are a few case reports in the literature in which the use of intravitreal Q-D has resulted in a favorable outcome without side ocular effects^[5-6]. However to date, there are no published data on retinal toxicity of intravitreal Q-D using histopathology or electroretinographic studies.

The purpose of this study is to determine the safety of different Q-D doses administered in the vitreous of rabbit eyes.

MATERIALS AND METHODS

All experimental procedures in this study comply with the statutes for care and handling of animals of the Association for Research in Vision and Ophthalmology (ARVO); all care, production and experimental animal use followed the official Mexican standard NOM-062-ZOO-1999 guidelines; biological waste was disposed of in compliance with the standard NOM-087-ECOL-94 laws. The study protocol was approved by the Ethics Committee and Review Board of the Association for Prevention of Blindness Hospital, Mexico City, Mexico.

Eighteen New Zealand white rabbits (weighing approximately 2500 g each) were used and randomly assigned to study groups 1, 2, and 3 (six eyes per treatment group). The 18 eyes were randomly distributed to receive 1 of 3 different intravitreal doses in the right eye: group 1 received 0.1 mg/0.1 mL; group 2 received 1 mg/0.1 mL and group 3 received 10 mg/0.1 mL. In every subject, the right eye received the Q-D injection, while the left eye served as its control.

The rabbits were sedated with an intravenous ketamine dose of 10 mg/kg (King Pharmaceutical, Inc., Bristol, TN, USA) and a topical dose of 5 mg/mL of proparacaine (Sophia Laboratories, Inc., México city, TX, USA). After sedation, 0.1 mL of the corresponding concentration of Q-D was injected into the right eye, and left eye received intravitreal injection of 5% dextrose water and served as control eye. Intravitreal injection was performed under sterile conditions, using a 27 gauge needle, in the temporal sclera as the injection site.

Solution Preparation and Administration A 500 mg single dose Q-D vial was reconstituted under aseptic conditions under a laminar air flow hood, by slowly adding 5 mL of 5% dextrose in water. The vial was then manually stirred by rotational movements to avoid foam formation. The resultant concentration of the Q-D solution was 100 mg/mL.

The reconstituted solution was diluted again within 30min in 5% dextrose solution to obtain the appropriate concentrations assigned to each group (group 1: 0.1 mg/0.1 mL; group 2: 1 mg/0.1 mL and group 3: 10 mg/0.1 mL) for injection. As indicated by the manufacturer, injections were applied at room temperature and within 1h of preparation to ensure stability of the drug. Treatment was administered slowly and under direct visualization-in the mid-vitreous of each eye, with the bevel of the needle positioned upwards.

After 28d, all rabbits were euthanized with an overdose of intravenous sodium pentobarbital (0.36 mg/kg) and the eyes were enucleated and stored in 15 mL 10% formalin until histological preparation.

Ophthalmoscopic Studies All eyes were examined on the day before treatment (day 0) and on days 7, 14, 21 and 28. Thirty minutes before examination, the pupils were dilated with 2 drops of 0.5% tropicamide and 15min later, with 0.5% phenylephrine hydrochloride. The eyes were examined by indirect ophthalmoscopy and were photographed (FF 450 plus, IR, AVTZK5, Carl Zeiss, Germany).

Electroretinography Simultaneous bilateral electroretinography (ERG) was performed prior to injection and 1, 2, 3 and 4wk after injection in all 18 rabbits.

Under a dim red light, the rabbits were anesthetized and one drop of topical anesthesia was applied in each eye. The pupils were dilated with 2 drops of 0.5% tropicamide and 0.5% phenylephrine hydrochloride 15min later, 30min before the study. Two recording electrodes (JET; LKC Technology, Gaithersburg, MD, USA) were placed in each eye *via* contact lenses and a ground electrode was placed on the forehead. The skin of the forehead had been previously shaved and cleaned, and a conductive cream was applied prior to electrode placement. Impedance was set to less than 5 ω in each electrode. The animals were adapted to the dark for 20min. After anesthesia induction, electrode placement and ERG recordings were performed under dim red light. White flashes to determine corneal electrical responses were delivered with a full-field Ganzfeld stimulator and Nicolet Ganzfeld amplifier (Nicolet, Madison, Wisconsin, USA); responses were measured and recorded in mesopic conditions. The a-wave and the b-wave were measured in all subjects. In compliance with the International Society for Clinical Electrophysiology (ISCEV) guidelines, the a-wave amplitude was measured from baseline to the a-wave's trough and the b-wave's amplitude was measured from the a-wave trough to the b-wave peak^[7]. A and b waves were measured in the scotopic 3.0 ERG phase.

Euthanization and Histological Study Animals were euthanized with an intravenous overdose of sodium pentobarbital (0.36 mg/kg). The animal's death was determined with the heart rate, respiratory rate and response to stimuli. Once the procedure was completed, the animal's eyes were enucleated and fixed in 10% neutral-buffered formaldehyde.

The globes were dissected horizontally and the calottes were processed and embedded in paraffin. Five-micrometer sections of the bisected globe were cut and evaluated by a pathologist unaware of the study's protocol. The anterior and posterior segments of the vitreous, nerve fiber layer, retinal ganglion cell layer, bipolar cell layer, photoreceptor layer, retinal pigment epithelium and choroid were evaluated for toxicity. For the sake of consistency, the same pathologist randomly reevaluated 25 slides.

The vitreous was directly examined in the histological slides and graded according to the presence of vitreous-retinal fibrovascular membranes as follows: Grade 0: absent membranes; Grade 1: membranes present in less than 25% of 10× power fields; Grade 2: membranes present in 25%-50% of 10× power fields; Grade 3: membranes present in 50%-75% of 10× power fields; Grade 4: membranes present in more than 75% of 10× power fields.

Retinal degenerative changes were graded as follows: Grade 0: the retina maintained its normal histological appearance and a normal number of ganglion cells; Grade 1: focal loss of histological architecture and partial loss of ganglion cells; Grade 2: loss of most ganglion cells and sectional loss of histological architecture; Grade 3: absence of ganglion cells and widespread loss of histological architecture-some remaining clumps of nuclear layers may be recognized.

The following observations were recorded: choroidal changes, congestion (due to optic nerve compression during enucleation), inflammation (lymphocytes), vacuolated histiocytes, foreign body giant cells and calcium deposition.

Statistical Analysis Data were analyzed with SPSS, version 20 for Mac; (SAS Institute Inc., Cary, NC, USA). Kruskal-Wallis test was used for intergroup analysis of the mean a and b wave amplitude values in the scotopic 3.0 ERG (maximal response phase). Friedman test was used for intragroup analysis. Mann-Whitney test was used for post-hoc comparisons. For all analyses, a 2-sided $P < 0.05$ was considered statistically significant.

RESULTS

Ophthalmoscopic Examination and Clinical Pictures All eyes were free of cataracts, vitreous opacities or bands at baseline examination (day 0). There were no significant differences between the injected and control eye in the group 1 throughout follow-up (Figure 1).

Vitreous opacities or band formation were not evident in any of the control eyes in all groups. In the treated eye in groups 2 and 3 (1 mg/0.1 mL and 10 mg/0.1 mL doses), vitreous opacities, various degrees of vitreous hemorrhage, retinal hemorrhages and vitreous bands were evident on the first post-injection examination, and on day 7 (Figure 2).

Electroretinography A total of 18 injected and 18 control eyes were analyzed. All subjects in the group 1 showed no signs of toxicity in the ERG when compared with control eyes. In the group 1, the a wave and b wave amplitudes in the injected eyes were stable, with no significant variation 4wk after injection (Figure 3).

All treated eyes in groups 2 and 3 showed no electrical response to light stimuli in the 3.0 scotopic ERG, 1wk after injection, reflecting severe retinal toxicity (Figure 4).

All subjects in groups 2 and 3 were euthanized after the first week and no further electrophysiological recordings were performed.

Subjects in the group 1 showed no signs of toxicity in the



Figure 1 Retinal fundus photograph of an injected eye of group 1. Optic nerve and vessels are normal appearance 21d after injection (0.1 mg/0.1 mL).

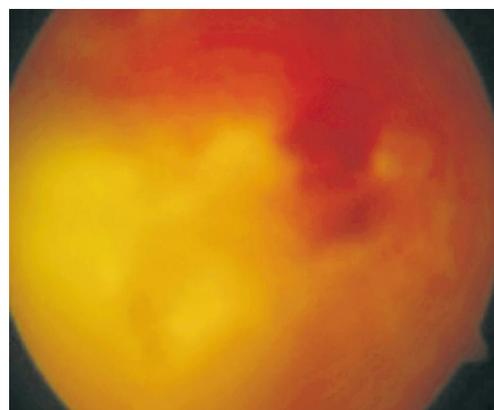


Figure 2 Retinal fundus photograph of an injected eye of group 2: 1 mg/0.1 mL, showing vitreous and retinal hemorrhages 21d after injection.

ERG when compared with groups 2 and 3 (Friedman test, $P = 0.000$). There was a statistically significant difference between the three groups ($P = 0.000$). ERG results are shown in Tables 1 and 2.

Histological Examination In a random and blinded manner, initial examination of sections obtained in group 1 showed integrity of all retinal layers, normal ganglion cell density and the presence of small caliber blood vessels in the inner limiting membrane of the posterior pole (these vessels have been described in the literature as normally present in the posterior pole retina of healthy rabbits). There were no pathologic changes observed in the outer retinal layers, nor in the retinal pigment epithelium. The anterior chamber and vitreous showed no anomalies. The choroid had some degree of congestion in all cases. Periodic acid-Schiff (PAS) and Gram stains were negative for microorganisms.

On the other hand, the eyes in groups 2 and 3 revealed pathologic changes in the vast majority. Five of the ten eyes showed some degree of congestion in the anterior segment. Vitreous examination revealed Grade 3 vitreoretinal

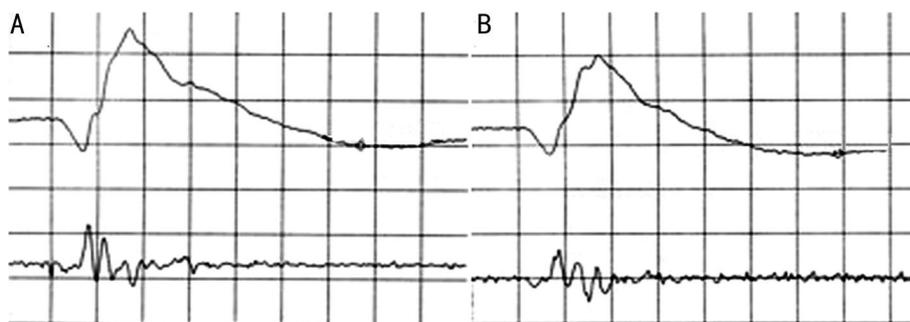


Figure 3 The a-wave amplitude in the 3.0 scotopic ERG of one injected eye of group 1 A: Scotopic ERG of group 1 in day 0; B :No significant variation at 4wk after injection. Sensitivity and sweep time per division: 100 μ V and 20ms.

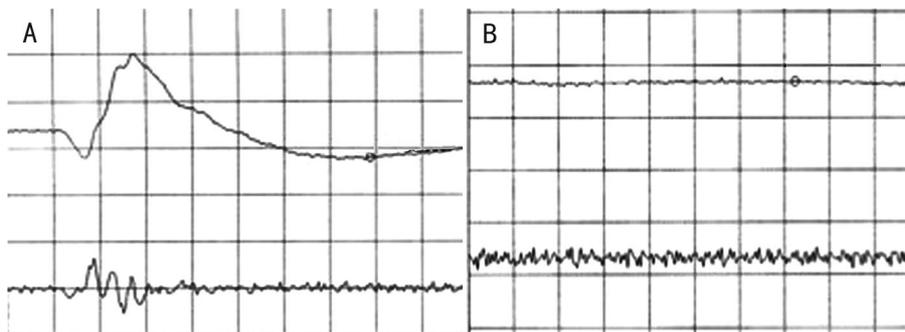


Figure 4 The a-wave and b-wave amplitudes in the 3.0 scotopic ERG of one injected eye of group 2 A: Scotopic ERG of one injected eye of group 2 in day 0; B: Abolition to light stimuli at 1wk after injection. Sensitivity and sweep time per division: 100 μ V and 20ms.

Wave amplitude	Baseline	Week 1	Week 2	Week 3	Week 4	mV; $\bar{x} \pm s$ <i>P</i>
Mean a-wave amplitude						
Group 1 (0.1mg)	46.8 \pm 37.8	68.7 \pm 16.7	53.1 \pm 9.4	45.8 \pm 17.5	43.7 \pm 17.2	0.373
Group 2 (1 mg)	40.9 \pm 14.7	0	-	-	-	0.000
Group 3 (10 mg)	45.27 \pm 6.7	4.5 \pm 9.1	-	-	-	0.006
Mean b-wave amplitude						
Group 1 (0.1 mg)	169.7 \pm 44.8	242.7 \pm 25.1	185.4 \pm 37.6	175 \pm 44	152 \pm 17.9	0.010
Group 2 (1mg)	109.9 \pm 45.1	0	-	-	-	0.000
Group 3 (10 mg)	143.1 \pm 24.1	0	-	-	-	0.000

Table 2 Comparisons of a-wave and b-wave amplitudes between treated eyes and control eyes

Wave amplitude	Treated eyes	Control eyes	<i>P</i>
Mean a-wave amplitude			
Group 1 (0.1mg)	52.8 \pm 17.6	57.2 \pm 24.6	0.876
Group 2 (1mg)	10.2 \pm 19.3	43.6 \pm 17.1	0.000
Group 3 (10 mg)	9.9 \pm 18.7	55.6 \pm 18.6	0.000
Mean b-wave amplitude			
Group 1 (0.1 mg)	188.8 \pm 45.8	167.1 \pm 39.9	0.072
Group 2 (1 mg)	32.9 \pm 56.6	131 \pm 54.7	0.000
Group 3 (10 mg)	33.1 \pm 60.5	129.7 \pm 63.9	0.000

membranes (6 eyes), and Grade 4 in 1 eye; extracellular foreign material vacuoles were observed in 5 eyes and histiocytic vacuoles with intracellular foreign material in 3 eyes.

Close examination of the choroid showed congestion, mild inflammation and vacuolated multinucleated giant cells in 7 eyes, 5 of which also had intracellular calcium deposits. Only 3 of 10 eyes had mild choroid congestion. All retinas in groups 2 and 3 had Grade 3 degenerative changes.

PAS staining showed vacuoles in histiocytes, granular material (calcium in some) in giant extracellular cells in 8 eyes and no remarkable features were observed in the other 2 eyes. Gram stain was negative to microorganisms.

In summary, there were no significant histopathological changes in the treated eyes of group 1 (Figure 5), while signs of granulomatous inflammation were found in most of the eyes of groups 2 and 3 (Figure 6). Image taken with light microscopy at high magnification with hematoxylin and eosin, showing the presence of calcium in the thickness of the retina, signs of granulomatous inflammation, and the presence of multinucleated giant cells of foreign body type, as well as degenerative changes. Image taken with light microscopy at medium magnification (10 \times) with hematoxylin and eosin illustrating retinal posterior pole with recent major bleeding and granulomatous reaction around extensive calcium deposition in the thickness of the retina with multiple degenerative changes. Note the presence of vitreous membranes (Figure 6).

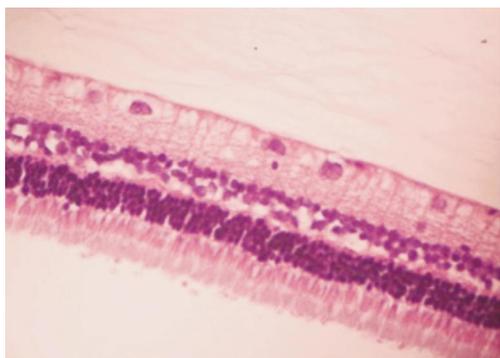


Figure 5 Histologic specimen of a treated eye of a rabbit from group 1 Intermediate histological image magnification (10×) with hematoxylin and eosin showing artificially detached retina. There is normal integrity of all layers with normal density of ganglion cells. No signs of inflammation nor vitreous membranes were observed.

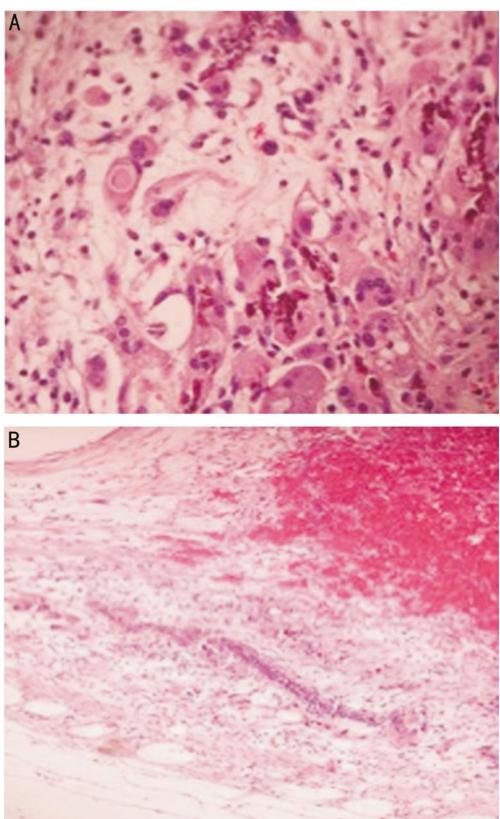


Figure 6 Histologic specimen of a treated eye of a rabbit from group 3 A: The presence of calcium in the retina, signs of granulomatous inflammation, and the presence of multinucleated giant cells of foreign body type; B: Retinal posterior pole with recent major bleeding and granulomatous reaction around extensive calcium deposition.

DISCUSSION

The introduction of intravitreal antibiotics revolutionized the treatment of infectious endophthalmitis, especially that due to bacteria. Several intravitreal antibiotics have been studied and used. Amikacin induces retinal toxicity as does intravitreal trovafloxacin; but others such as intravitreal garenoxacin appeared to be safe in an animal model and, levofloxacin appears to be effective in treating experimental endophthalmitis, but further studies are needed [8-12]. In a

recent review, the susceptibility, in endophthalmitis samples of bacterial isolates, to ceftazidime and vancomycin was studied and they conclude that they still remain the therapy of choice for this entity [11]. Nevertheless, because of the current high prevalence of bacterial resistance to vancomycin, and ceftazidime, treatment needs to be modified based on clinical response.

Novel antibiotics such as moxifloxacin and gatifloxacin, fourth-generation fluoroquinolones, have enhanced activity against Gram-positive bacteria while retaining potent activity against most Gram-negative bacteria, but intravitreal safety has not been demonstrated, and bacterial resistance was demonstrated in ocular samples [13-15].

Although many eyes are successfully treated with the use of intravitreal antibiotics-particularly when promptly administered-there are still many cases that do not respond adequately and have a poor visual outcome; this is partly due to the inflammatory phenomena occurring in endophthalmitis that are not quelled by intravitreal antibiotics alone. This is why some believe that the use of concomitant intravitreal steroids might be beneficial, although this therapeutic approach is still somewhat controversial [16].

Q-D is a streptogramin antibiotic that aside from its antibacterial properties. It has been shown to inhibit *in vitro* proinflammatory mediators such as IL-1 α , IL-1 β , IL-6 and TNF- α , suggesting a possible associated immunomodulatory activity [5]. These properties might be of some advantage when treating Gram-positive bacterial endophthalmitis versus conventional intravitreal therapy. There have been a few reports of intravitreal Q-D in humans with bacterial endophthalmitis resulting in favorable outcomes [5-6].

Hernandez-Da Mota [6] reported a successful single case using a dose of 0.4 mg/0.1 mL and Stroh [5] reported two successful cases of endophthalmitis caused by vancomycin-resistant strains, treated with a similar dose of Q-D. This is consistent with the findings in this study, where doses below 1 mg/0.1 mL did not lead to significant toxic effects in the studied eyes.

ERG showed no statistically significant differences between the amplitudes of the retinal a- and b-waves in rabbits injected with a low dose of Q-D (group 1) nor in control eyes, 2 and 4wk after injection. However, b-wave amplitude flattening and even a total loss of response were observed in groups 2 and 3, reflecting retinal toxicity. Also there was a more pronounced band formation in groups 2 and 3, which might be a sign of inflammatory response as well as toxicity.

Histological examination revealed no significant changes using doses of 0.1 mg/0.1 mL; however, granulomatous reactions were observed in the other two groups. These histopathological findings correlate with the electrophysiology results in the groups on doses above 1 mg/0.1 mL.

Retinal toxicity profiles have been conducted with other novel antibiotics. Kernt *et al* [14] reported that doses up to 150 μ g of moxifloxacin administered in the vitreous did not damage different retinal cells. Aydin *et al* [17] studying the

intravitreal toxicity of doxycycline, found that the group treated with the antibiotic exhibited significant decreases in the ERG with doses ranging between 250 and 2000 µg per 0.1 mL. No significant changes in the ERG were observed following the injection of lower doses [17]. Linezolid, a potent anti-staphylococcal antibiotic, is safe at a dose of 30 mg after intravitreal administration [18]. Daptomycin is reported to induce a total loss of the photoreceptor layer with doses of 750 µg, but doses up to 188 µg did not induce deleterious changes in the retina [19]. Comer *et al* [19] reported that intravitreal daptomycin doses above 200 µg resulted in ERG abnormalities, while doses between 75 and 188 µg did not lead to changes in the scotopic and photopic waves of the ERG; moderate depression was exhibited in the 375 µg dose range, and severe depression resulted with the 750 µg dose.

This study has numerous limitations that must be considered. The small number of animals used (6 for each group) could mask a possible real difference (type 2 statistical error). Since no statistically significant difference in electroretinographic activity between Q-D and control eyes was found in the low dose group, careful attention to the power of the study is required, specially assuming that a clinically insignificant change in electroretinographic activity would be less than a 20% difference between wave amplitudes.

There are some issues that remain unsolved. It is unknown whether doses between 0.1 mg/0.1 mL and 1 mg/0.1 mL are toxic. This should be interesting since successfully treated cases of endophthalmitis managed with Q-D fall within this dose range [5-6]. Further animal studies may be necessary to determine this factor. However, based on these results and what has been previously reported, it seems that the window of Q-D intraocular toxicity might not be as narrow as other antibiotics that have been administered into the vitreous such as amikacin. Whether these doses have an adequate antibacterial activity with the levels reached in the vitreous cavity, retina and choroid also remains to be determined.

Further studies will also be needed on the Q-D minimum inhibitory concentrations *in vitro* followed by animal induced endophthalmitis models to prove its safety and efficacy as well as its pharmacokinetic characteristics. Another question arising with the use of Q-D in infectious endophthalmitis is whether combining it with other antibiotics might provide additional benefits. This issue should also be addressed in further studies since it has already been confirmed in other systemic infections [4]. Comparative animal endophthalmitis model studies also need to be conducted with standard intravitreal antibiotics such as vancomycin and ceftazidime. These issues need to be addressed in order to further assess the role of intravitreal Q-D in human bacterial endophthalmitis.

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Salinas –Longoria SM, None; **Romero –Vera R**, None; **Jimenez–Sierra JM**, None; **Guerrero–Naranjo JL**, None; **Morales–Canton V**, None.

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