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INTRAVITREAL DAPTOMYCIN: A SAFETY AND EFFICACY STUDY

Grant M. Comer, MD, John B. Miller, MD, Eric W. Schneider, MD, Naheed W. Khan, PhD, David M. Reed, PhD, Victor M. Elner, MD, PhD, and David N. Zacks, MD, PhD

University of Michigan, Department of Ophthalmology and Visual Sciences, 1000 Wall St, Ann Arbor, MI 48105, Phone: (734)763-7711, Fax: (734) 936-2340

David N. Zacks: davzacks@umich.edu

Abstract

Purpose—To determine the ocular toxicity of intravitreally injected daptomycin, a novel antibiotic for treatment of vancomycin-resistant organisms, and its efficacy in treating intraocular infection with coagulase-negative *Staphylococcus epidermidis*.

Methods—Toxicity study: Four doses of intravitreal daptomycin were injected (75, 188, 375 and 750 micrograms) into one eye of Dutch belted rabbits (n=3 per dose). Clinical examination, electroretinography (ERG) and histologic analysis was performed pre-injection and two-weeks after injection and compared to the fellow eye that received only intravitreal balanced salt solution. Efficacy study: Experimental *S. epidermidis* endophthalmitis was induced in Dutch belted rabbits (n=24) and the ability of 200 micrograms of intravitreal daptomycin to result in culture-negative vitreous samples was measured at 24 and 48 hours.

Results—Toxicity: 75 and 188 micrograms of daptomycin demonstrated acceptable safety profiles when injected intravitreally in Dutch belted rabbits. There was a dose-dependent increase in cataract formation, ERG suppression and photoreceptor damage with higher doses. Efficacy: 200 micrograms of intravitreal daptomycin resulted in near complete vitreous sterilization 24 hours following treatment. Vitreous sterilization was complete by 48 hours.

Conclusions—A dose of 200 micrograms of intravitreal daptomycin appears to be safe and efficacious in a rabbit model of bacterial endophthalmitis. Future investigations should focus on daptomycin as a therapeutic option for treating intraocular infection caused by vancomycin-resistant organisms.

Keywords

Daptomycin; Endophthalmitis; Antibiotic Resistance

INTRODUCTION

Acute post-operative bacterial endophthalmitis is a visually devastating intraocular infection of increasing prevalence and incidence.^{1–6} The Endophthalmitis Vitrectomy Study (EVS), a National Eye Institute-sponsored, multicenter, randomized controlled trial of 420 subjects with acute post-operative bacterial endophthalmitis, reported that, despite treatment, 47% of affected eyes failed to achieve a final Early Treatment Diabetic Retinopathy Study (ETDRS)

Correspondence to: David N. Zacks, davzacks@umich.edu.

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chart visual acuity of 20/50, commonly cited as the reading and legal driving threshold, and 15% had a nonfunctional acuity worse than 5/200 or required enucleation.⁷

Traditionally, clinicians have used intravitreal vancomycin against Gram-positive organisms because of superior broad-spectrum coverage, minimal resistance, acceptable rates of intraocular sterilization, and a lack of toxicity.⁸ Although vancomycin resistance in endophthalmitis is limited to a few case reports,^{9–12} several recent publications have reported increasingly poor sensitivity to vancomycin in non-ocular infections caused by common Gram-positive endophthalmitis isolates including *Staphylococcus*^{13–16}, *Streptococcus*^{17–19}, and *Enterococcus*^{20,21} species.

Newer antibiotics, indicated for vancomycin-resistant Gram-positive infections, are commercially available. However, published studies have not sufficiently evaluated their safety and efficacy in the eye. Of these antimicrobials, daptomycin appears to provide the greatest opportunity of providing both a viable treatment alternative and improving final outcomes. This pre-clinical study will explore the safety and efficacy of daptomycin for treating bacterial endophthalmitis in a rabbit model.

METHODS

All animal work conformed to the Association for Research in Vision and Ophthalmology (ARVO) statement on animal use and received approval from the University Committee on Use and Care of Animals (UCUCA) at the University of Michigan. The intraocular toxicity of daptomycin was first assessed to establish a threshold dose. The largest safe dose of daptomycin was then used to study its efficacy in experimentally induced endophthalmitis.

Toxicity Study

Twelve adult male Dutch Belted rabbits (2.2–2.5 kg) were divided into four treatment groups, each receiving a different dose of daptomycin as defined below. Dutch Belted rabbits were chosen because they have a pigmented RPE, a potential risk factor for increased toxicity^{22–24}. All the rabbits were anesthetized with intramuscular ketamine hydrochloride (22–50 mg/kg), xylazine hydrochloride (2.5–10 mg/kg), and atropine sulfate (0.04–2.0 mg/kg) and topical proparacaine hydrochloride 0.5%, phenylephrine 2.5%, and tropicamide 1% were applied to both eyes. A baseline clinical examination and standard Ganzfeld dark- and light-adapted electroretinogram (ERG) were performed on each eye followed by an injection of daptomycin into the right eye. Vehicle alone was injected into the left eye as a control.

Clinical examination—An eyelid speculum was placed between the lids and indirect ophthalmoscopy with a 20 diopter lens was used to assess the anterior and posterior segment structures for abnormalities. Any abnormalities were listed in a qualitative fashion.

Electroretinography—Rabbits were anesthetized and dark-adapted for one hour. Each rabbit was placed on a hand-crafted gurney supporting the body, with the head in the natural upright position. A water blanket was placed beneath the rabbit and attached to a Gaymar T/Pump (Gaymar Industries, Orchard Park, NY) set at 103 °F (39 °C). The gurney was then slid into a large Ganzfeld bowl (LKC Technologies, Inc., Gaithersburg, MD). Core body temperature was maintained between 101–103 °F (38–39 °C) using a rectal thermometer (Thermalert Model TH-8 Temperature Monitor with Ret-1 probe, Physitemp Instruments, Inc., Clifton, NJ). Following topical corneal anesthesia (0.5% proparacaine) and lubrication with methylcellulose, bipolar contact lens electrodes (size U18, Mayo Corporation, Aichi, Japan) were placed on each eye. The grounding needle electrode was placed subcutaneously on the scruff.

ERGs were recorded with a Ganzfeld configuration using the Espion e² electrophysiology system (Diagnosys LLC, Lowell, MA). Brief xenon white flashes were elicited from a photostimulator (PS-22, Grass Technologies, West Warwick, RI). Responses were amplified at 1,000 gain at 1.25–1000 Hz, and digitized at a rate of 2000 Hz. A notch filter removed 60 Hz line noise. Scotopic ERGs were recorded at dim stimuli ($-1.82 \log \text{cd-s/m}^2/\text{flash}$) and at maximum intensity ($1.09 \log \text{cd-s/m}^2/\text{flash}$), and 5 to 10 responses at each intensity were computer averaged. Stimulus intensity was adjusted using Kodak Wratten (Eastman Kodak Co., Rochester, NY) neutral density filters. Following 10 minutes of light adaptation on a continuous light adapting white background of 34 cd/m^2 , photopic ERGs were recorded at maximum flash intensity ($1.09 \log \text{cd-s/m}^2/\text{flash}$).

Intraocular injection—Using sterile technique, the periocular tissues were scrubbed with a 5% povidone-iodine solution. An eyelid speculum was inserted and the eye was infraducted to expose the injection site. 5% povidone iodine was placed on the ocular surface and a 30-gauge needle on a 1 mL tuberculin syringe was inserted into the mid-vitreous cavity at a distance 2.5 mm posterior to the limbus. The right (experimental) eye received one of the following four doses of daptomycin (Cubist Pharmaceuticals, Lexington, MA): 75, 188, 375, or 750 micrograms (μg) in a volume of 0.05 mL of sterile intraocular balanced salt solution (BSS®, Alcon Laboratories, Ft. Worth, TX). As a control, the left eye of each animal received 0.05 mL of BSS® solution.

After 14 days, each rabbit was again anesthetized, clinically examined, and underwent repeat ERG. The animals were sacrificed with intracardiac pentobarbital sodium (200–300 mg/kg); both eyes were enucleated and processed for histopathology.

Histopathology—After enucleation, the eyes were immediately placed into 4% formaldehyde (pH 7.2) and stored at 4 °C. Eyes were processed with paraffin embedding, sectioned at 8 micron thickness, stained with hematoxylin, and counterstained with eosin. Eyes were graded by a masked independent reader (V.M.E.) who qualitatively assessed the sectioned globes.

Efficacy Study

Twenty four adult male Dutch Belted rabbits (2.1–2.4 kg) were divided into four treatment groups (Groups A–D) consisting of eight experimental rabbits in Groups A and B and four control (natural history) rabbits in Groups C and D (Table 1). All the rabbits were anesthetized as above. Buprenorphine (0.01–0.05 mg/kg) was injected subcutaneously every 8 hours until the rabbit was sacrificed for pain control.

A clinical assessment was performed on each eye followed by a 0.1 mL injection of approximately 2×10^5 colony forming units of *Staphylococcus epidermidis* (American Type Culture Collection [ATCC] No. 12228; ATCC, Manassas, VA) into the vitreous cavity of the right eye and normal saline control vehicle into the left eye as previously described. Residual bacterial solution was plated on blood agar for confirmatory cultures and sensitivities.

After 24 hours, all rabbits were anesthetized and the eyes were again clinically graded. The right eyes of Groups A and B received an intravitreal injection of 200 μg daptomycin diluted with BSS® while Groups C and D received an injection of BSS®. The left eyes of all rabbits received 200 μg of daptomycin diluted with BSS®.

At 48 hours, all rabbits were graded clinically and the rabbits in Groups A and C with euthanized. The eyes were enucleated and the vitreous of both eyes was cultured.

At 72 hours, both eyes of the surviving rabbits (Groups B and D) were graded clinically and each rabbit was then euthanized. The eyes were enucleated and the vitreous was cultured.

Clinical examination—An eyelid speculum was placed between the lids and indirect ophthalmoscopy with a 20 diopter lens was used to assess the anterior and posterior segment structures for signs of inflammation or toxicity. Conjunctival injection, corneal clouding, hypopyon, cataract, and vitritis were graded by a single masked grader (D.N.Z) on a scale of 0 to 4, with zero indicating normal findings and increasing values corresponding to increasing severity of abnormal findings. Any other abnormalities were listed in a qualitative fashion. The clinical inflammatory scores were compared with a two-sample, two-tailed Student's t-test (SAS Institute, Inc., Cary, NC).

Bacterial preparation—Bacteria were grown in trypticase soy broth (TSB), 30 g BBL TSB powder per liter (Becton Dickinson and Company, Sparks, MD), and all procedures followed standard, sterile microbiological techniques. After incubation overnight at 37 °C, the bacteria were diluted in TSB. Based on empirically determined growth curves, bacteria were grown to mid-loggrowth phase. The log-growth phase for 6×10^7 colony forming units per mL was equivalent to an optical density reading of 0.4 at 625 nm on a spectrophotometer (Shimadzu UV-2401 PC; Shimadzu Scientific Instruments, Columbia, MD). Serial dilutions were made in sterile isotonic sodium chloride solution to achieve the desired bacterial count per 0.1 mL. Counts were verified by plating aliquots of the serially diluted samples on TSB agar (30 g/L BBL TSB powder, 15 g/L granulated agar [Fisher Chemicals, Fairlawn, NJ]), which were incubated overnight at 37 °C.

Vitreous cultures—After enucleation, an area was demarcated 2.5 mm posterior to the limbus. After painting the area with a povidone iodine swab, a 20 gauge needle on a 3 mL syringe was inserted into the mid-vitreous cavity where approximately 0.5 mL of material was aspirated. The material was then dripped onto a blood agar plate where it was spread over the plate with the solid end of a sterile cotton tipped applicator. The culture plates were inoculated at 37 °C for 72 hours and graded as follows: 0 = no growth, 1 = 1–10 colony forming units (mild growth), 2 = more than 10 colony forming units (significant growth).

A single rabbit was euthanized before conclusion of the study in Group A (anesthesia overdose) and Group B (injured hindquarters).

RESULTS

Toxicity Study

Clinical examination—The baseline clinical examination revealed normal ocular structures including conjunctiva, cornea, anterior chamber, lens, and vitreous in both eyes of all rabbits. The experimental right eye of two rabbits injected with 750 µg and one rabbit receiving 375 µg of daptomycin developed dense white cataracts by day 14. The exam of all other experimental right and control left eyes was unremarkable.

Electroretinography—The scotopic and photopic waveforms exhibited no change in the 75 and 188 µg daptomycin doses, moderate depression in the 375 µg dose, and severe depression with the 750 µg dose compared with baseline. Implicit times were variable but generally unchanged at all the doses. All control eyes exhibited normal waveforms and implicit times between baseline and day 14 on electroretinography (Figures 1 and 2).

Histopathology—The photoreceptor layer was preserved in all control eyes and the 75 µg and 188 µg daptomycin doses, moderately reduced in the two of three 375 µg doses, and

entirely absent in two of three 750 µg doses. All control eyes and daptomycin-injected eyes demonstrated vacuolization of the ganglion cell layer. Given the presence of ganglion cell layer vacuolization in both experimental and control eyes, we attributed it to processing artifact. All other posterior structures, including the retinal pigment epithelium, appeared normal in all eyes (Figure 3).

Efficacy Study

Clinical examination—At baseline, all eyes scored zero on the clinical inflammation grading scale. At 24 hours after inoculation, the average inflammatory scores in all experimental eyes were elevated over baseline but not significantly different among the four treatment groups ($p>0.05$). At all time points thereafter, there were no differences in the inflammatory scores between the daptomycin treated groups and natural history groups ($p>0.05$). The inflammatory score of all left control eyes remained zero throughout the study.

Cultures—Cultures of the bacterial suspension were independently confirmed by the University of Michigan Microbiology lab as *Staphylococcus epidermidis* and sensitive to daptomycin at an MIC₉₀ of 0.5 µg/mL. Vitreous cultures of all control left eyes demonstrated no growth. At 48 hours after inoculation, vitreous cultures of the right eye, which received daptomycin 24 hours previously, revealed significant growth in 2/7 eyes, mild growth in 4/7 eyes, and no growth in 1/7 eyes. No growth in any infected eye (0/7) was observed at 48 hours after antibiotic injection. Untreated eyes all showed significant bacterial growth at both time points.

DISCUSSION

Our study shows that intravitreal daptomycin, at a dose of 200 µg, is safe and effective in an adult pigmented rabbit eye model of endophthalmitis. As the MIC₉₀ for the most common endophthalmitis isolates ranges from >1 µg/mL to 8 µg/mL, with the upper limit corresponding to the value for *Enterococcus*, which represents the most difficult genera to eradicate, the largest tolerated dose is in excess of 15 times the MIC₉₀. However, the safe therapeutic window is narrow as doubling the dose resulted in severely depressed ERG waveforms and photoreceptor dropout.

Therapeutically, uniform intraocular sterility was achieved. However, completely negative cultures were not observed until 48 hours after intravitreal daptomycin administration. The clinical inflammatory scores progressed in a similar fashion in both the daptomycin-treated eyes and the untreated natural history eyes. To our knowledge, no reports have described the rate or degree of intraocular sterility using vancomycin in a similar model. The persistent intraocular inflammation after treatment could be related to local loculation of the daptomycin around the injection site. There could also be a low concentration of intraocular calcium ions or high concentration of proteins known to bind daptomycin thus reducing its efficacy (see discussion below). Unknown factors related to the poor retinal vasculature of rabbit eye could also contribute to the delayed therapeutic effect and progressive inflammatory response.

The treatment paradigm for post-operative endophthalmitis has remained relatively static since the Endophthalmitis Vitrectomy Study was published in 1995.^{8, 9, 25, 26} In that study, 94% of culture-positive isolates were Gram-positive and intraocular vancomycin is highly effective towards eliminating these infections. To date, only a several isolated cases of vancomycin-resistant endophthalmitis have been reported.^{9–11} However, frequently poor clinical outcomes and increasing extraocular vancomycin-resistance suggest that vancomycin may not be the ideal antibiotic for Gram-positive infections in the eye.

Clinically, poor outcomes are commonly encountered in enterococci, *S. aureus*, and streptococci-mediated endophthalmitis despite the use of vancomycin with seemingly adequate sensitivities.^{7,25} While vancomycin is bactericidal against many staphylococci and streptococci isolates, it is often simply bacteriostatic against *Enterococcus faecalis* and *E. faecium* in addition to some *Staphylococcus aureus* isolates. Also, the rate of bactericidal activity against *Streptococcus pneumoniae* is alarmingly slow.^{27–29} In these latter instances, vancomycin might halt bacterial growth but require an intraocular immune response to ultimately eliminate the infection. While there may be a destructive aspect to the infiltration of immune cells, these same cells may play an important role in clearing the eye of the harmful organism. The necessity of intraocular immune infiltration could also explain the equivocal, and at times harmful, outcomes encountered when augmenting the antibiotics with immunosuppressants, such as intravitreal dexamethasone.^{30–32}

Compared to vancomycin, daptomycin demonstrates superior *in vitro* bactericidal activity for antibiotic-susceptible and resistant strains of bacteria accounting for endophthalmitis including: *S. epidermidis*, *S. aureus*, *S. pneumoniae*, *E. faecalis*, and *E. faecium*.^{33–36} It kills 99.9% of Gram-positive bacteria within 6–8 hours compared to 12–24 hours or simple bacteriostasis achieved with vancomycin.³³ The concentration-dependent depolarization of the bacterial cytoplasmic membrane inhibits protein synthesis, which prevents cell lysis and averts the release of proinflammatory and toxic byproducts.^{37–41} In addition, it kills bacteria in both the stationary and exponential growth phases.⁴² In a rabbit ventriculitis model, which simulates the immunoprotected environment of the eye, daptomycin achieved superior bactericidal activity, more rapid kill-times, and a longer half-life.⁴³

Despite these many advantages, the use of daptomycin for an endophthalmitis indication has some potential limitations. It is unknown how the intraocular toxicity profile will translate to the human eye, which has a larger vitreous cavity and increased retinal vascularity as compared to the rabbit eye. Therapeutically, the activity of daptomycin is strongly dependent on calcium ions.⁴⁴ In humans, the mean vitreous calcium concentration is maintained by an active transport mechanism at between 6.8–7.2 milligrams (mg)/deciliter (dL) while the mean serum concentration is 9.6 mg/dL.^{45–48} In addition, 90–94% of daptomycin is proteinbound to mostly albumin and alpha₁-acid glycoprotein, which might limit the therapeutic free drug available.^{49,50}

In summary, intravitreal daptomycin at a dose of 200 ug appears to be safe and efficacious in a rabbit model of bacterial endophthalmitis. The therapeutic window appears narrow and uniformly negative cultures were not achieved until 48 hours after administration of the intravitreal daptomycin. While daptomycin could be considered in a case of culture-proven vancomycin-resistant endophthalmitis, further work is required before it can be recommended for routine use as a standard therapeutic agent in humans.

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SUMMARY STATEMENT

Intravitreal daptomycin at a dose of 200 ug appears to be safe and efficacious in a rabbit model of bacterial endophthalmitis. Daptomycin could be considered in cases of culture-proven vancomycin-resistant endophthalmitis. Further work is required before it can be recommended for routine use as a standard therapeutic agent in humans.

Figure 1.

Representative ERG tracings for the scotopic (rod) response (left panel), mixed (bright-flash response) (middle panel), and photopic (light adapted) response (right panel). The baseline tracing is in red and the tracing after 14 days is in blue for the right (daptomycin) and left (control) eyes from each group.

Figure 2.

Mean amplitudes for various ERG parameters as a function of daptomycin dose for animals in Groups 1–4 at baseline and 14 days. For all parameters measured, there was a significant decrease in the eyes receiving 375 or 750 µg of daptomycin (asterisk denotes p value <0.05). There were no changes in any of the ERG parameters in eyes receiving control injection.

Figure 3.

Histopathology of the retina in eyes receiving increasing doses of daptomycin. There is marked loss of photoreceptors with the 375 and 750 µg doses of daptomycin. The retina in the the 75 µg dose is not shown, as it is normal and essentially the same as for the 188 µg dose. Note that the retinal pigment epithelial and choroidal layers are absent in some of the photomicrographs due to artifactual separation during tissue processing. (Abbreviations: GCL- Ganglion Cell Layer; INL-Inner Nuclear Layer; ONL-Outer Nuclear Layer; PRL- Photoreceptor Cell Layer).

Table 1

Overview of time course for experimental eyes.

Time	t=0	t=24h	t=48h	t=72h
Group A (n=7)	Bacteria	Dapto	Sac + Vit Cx	----
Group B (n=7)	Bacteria	Dapto	Exam	Sac + Vit Cx
Group C (n=4)	Bacteria	BSS	Sac + Vit Cx	---
Group D (n=4)	Bacteria	BSS	Exam	Sac + Vit Cx

Bacteria = inoculation with 2×10^5 *Staphylococcus epidermidis*; Dapto = injection of 200 ug of daptomycin; BSS = Balanced Salt Solution; Sac and Vit Cx = Sacrifice and Vitreous Culture