

Concentrated Intravitreal Amphotericin B in Fungal Endophthalmitis

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Objective: To describe the clinical courses of patients who received intravitreal injections of highly concentrated amphotericin B deoxycholate for suspected fungal endophthalmitis.

Methods: Retrospective medical record review of 3 cases of intraocular toxicity from highly concentrated amphotericin B.

Results: The first patient developed posttraumatic endophthalmitis and received an undiluted dose (500 µg) of amphotericin B. He developed severe intraocular inflammation and required a pars plana lensectomy, vitrectomy, and scleral buckle after developing a cataract and retinal detachment. Six years later, his visual acuity stabilized at 20/30. The second patient developed endogenous endophthalmitis and was treated with 5 intravitreal injections of amphotericin B and underwent 3 surgical procedures. The surgeon later discovered that the patient had received 55 µg of amphotericin B during the second injection. Three months af-

ter the injection, the patient's visual acuity was 20/60. The third patient developed chronic postoperative endophthalmitis following cataract extraction. He received 160 µg of amphotericin B and was immediately treated with a vitreous washout. Two years later, his visual acuity improved to 20/30. The vitreous culture results were negative in each case. A key finding was that the amphotericin B solution appeared to be yellow instead of nearly colorless.

Conclusions: We present 3 cases of intraocular toxicity from highly concentrated amphotericin B. In every case, the overly concentrated amphotericin B solution was yellow in color. Although severe noninfectious panophthalmitis resulted in every case, the visual acuity outcomes were good. Physicians should examine the color of amphotericin B solution prior to intraocular administration. If the solution appears to be yellow, the medication should not be injected.

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ENDOPHTHALMITIS, A SEVERE and often sight-threatening infection of the intraocular fluids or tissues, is typically caused by bacteria and less commonly caused by fungi.¹ Exogenous fungal infections of the eye are a well-recognized complication of trauma and surgery, and endogenous fungal endophthalmitis remains a serious problem for immunocompromised patients. The treatment of fungal endophthalmitis continues to represent a significant challenge for ophthalmologists, principally because the diagnosis is often challenging, there are a limited number of therapies available, and the outcomes are frequently unfavorable.²⁻⁴

Although newer medicines, such as voriconazole, have been used to treat fungal endophthalmitis, amphotericin B deoxycholate has remained the treatment of choice for fungal endophthalmitis.^{5,6} Amphotericin B is effective against a wide

range of fungal pathogens, but its utility in treating fungal endophthalmitis is limited by poor ocular penetration and the potential for intraocular toxicity.⁵⁻⁹ Intravitreal doses of 5 to 10 µg of amphotericin B have been used increasingly since Axelrod et al⁸ found that these doses did not cause clinical, histopathologic, or electroretinographic changes in rabbit eyes. Although these doses are generally well tolerated, another study⁹ showed that retinal damage can occur with doses as low as 1 µg. The 2 studies^{8,9} agreed that intravitreal doses greater than 25 µg were extremely toxic and may cause profound intraocular inflammation, retinal necrosis, and cataract formation. To our knowledge, there have been no reported cases of human patients who have been accidentally treated with intravitreal injections of toxic doses of amphotericin B. The purpose of this case series is to describe the clinical course and outcomes of pa-

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Table. Clinical Outcomes of Patients Who Were Treated With Highly Concentrated Amphotericin B

Case No.	Culture/Results	Actual Dosage, µg	Initial Visual Acuity, Snellen Fraction	Final Visual Acuity, Snellen Fraction	Toxic Effects	Treatment After Intravitreal Injection of Highly Concentrated Amphotericin B
1	Vitreous/negative	500	20/60	20/30	Cataract, RD with PVR, panophthalmitis	Lensectomy and PPV 2 days after infection; scleral buckle at 1 month; another PPV and endophotocoagulation at 2 months
2	Blood/positive for <i>Candida albicans</i> ; vitreous/negative	55	CF	20/60	Cataract, RD, panophthalmitis	Lensectomy, PPV, and another injection on day 1; another injection on day 3; another PPV and injection on day 4
3	Vitreous/negative	160	20/30	20/30	Panophthalmitis	PPV and vitreous washout on day 1

Abbreviations: CF, counting fingers; PPV, pars plana vitrectomy; PVR, proliferative vitreoretinopathy; RD, retinal detachment.

tients who were treated with highly concentrated doses of amphotericin B for fungal endophthalmitis. In addition, all cases could have been recognized by the color of the solution being injected.

METHODS

After receiving approval from the Emory University School of Medicine institutional review board, we retrospectively reviewed the medical records of 3 patients who had been diagnosed with fungal endophthalmitis and subsequently treated with intravitreal injections of highly concentrated amphotericin B. The demographic information, age at presentation, symptoms, and ocular and medical history were recorded for each patient. The treatment regimens (both medical and surgical) and the results of the microbiological laboratory tests were recorded. Visual acuity (using the Snellen eye chart) at presentation and last follow-up and the ophthalmic findings during the treatment course were also documented.

The mechanism for the development of endophthalmitis was different in all 3 patients. The first patient had suspected traumatic exogenous fungal endophthalmitis, the second patient developed bilateral endogenous fungal endophthalmitis, and the third patient presented with chronic postoperative fungal endophthalmitis following cataract extraction. The treating physicians were all suspicious of an incorrect dose of amphotericin because of the color of the solution. Each patient was immediately informed of the dosing error once the error had been confirmed.

RESULTS

A summary of the clinical outcomes of the 3 patients are shown in the **Table**.

CASE 1

An 11-year-old boy presented 10 days after being struck in the left eye by a dart. His visual acuity was 20/60, and he had a sealed corneal perforation site inferotemporally near the limbus and peripheral cortical changes in the lens. Moderate anterior chamber and vitreous inflammation was present. He was taken to the operating room immediately for an anterior chamber paracentesis and vitreous biopsy for a presumptive diagnosis of delayed onset traumatic endophthalmitis. He received intravitreal injections of amikacin (dose, 400 mg), vancomycin (dose, 1 mg), and amphotericin B (dose requested

was 5 µg/0.1 mL). The surgeon inspected the amphotericin prior to injection and noted that it was “bright yellow.” The pharmacist, who was contacted, reassured the surgeon that amphotericin B is yellow and that the dosing was correct. The medication was therefore injected. On the first day after surgery, the boy’s visual acuity decreased to counting fingers. There was a marked increase in vitreous inflammation and a new lenticular opacity. He was taken back to the operating room 2 days after surgery for a pars plana vitrectomy, lensectomy, and intravitreal injection of clindamycin (dose, 400 mg). Large amounts of vitreous debris were removed, and it was noted that the macula appeared whitish and pale. Subsequently, the pharmacy discovered that the delivered syringe contained undiluted amphotericin B (500 µg/0.1 mL) at the time of initial intravitreal injection.

The patient’s condition slowly began to improve after surgery, and 2 weeks later, his vision was correctable to 20/200. At that time, he was noted to have lipid deposits and pigmentary changes present in the macula. His vitreous culture results remained negative. One month after presentation, his vision had diminished to the hand motion level, and he was found to have an inferior rhegmatogenous retinal detachment. He underwent an uneventful scleral buckling procedure the following day. During the following month, his visual acuity slowly improved again to 20/200, but he had developed persistent subretinal fluid inferiorly and proliferative vitreoretinopathy. He underwent another vitrectomy in conjunction with epiretinal membrane peeling, air-fluid exchange, and endophotocoagulation. One month after this last surgery (3 months after presentation), his retina was attached and his visual acuity was correctable to 20/80. The patient was eventually fitted for a contact lens in the left eye, and 6 years later, his visual acuity had stabilized at 20/30.

CASE 2

A 45-year-old man presented to the retina specialist 3 weeks after developing a febrile illness. The patient had initially been treated at a remote hospital for fungemia due to a blocked ureter. Results of blood cultures during the initial hospitalization were positive for *Candida albicans*. On presentation to a local ophthalmologist, he reported having decreased vision in the right eye. The ophthalmologist suspected fungal endophthalmitis and

referred the patient to a retina specialist for further evaluation. On examination, his visual acuity in the right eye was limited to counting fingers, and his visual acuity in the left eye was 20/20. The results of his fundoscopic examination revealed marked vitritis in the right eye. There was a prominent white, fluffy lesion attached to the retina superior to the fovea. The retina was attached. The left eye also contained multiple white lesions on the retina, none of which involved the macula. There was no vitritis in the left eye.

The patient underwent a pars plana vitrectomy, and specimens of the vitreous of the right eye were obtained for presumed endogenous fungal endophthalmitis. Amphotericin B (dose, 5 µg/0.1 mL) was injected into the vitreous cavity of the right eye. The patient was hospitalized for intravenously administered antifungal treatment. On the third day after surgery, the right eye had developed increased vitreous inflammation. A second intravitreal injection of amphotericin B (dose, 5 µg/0.1 mL) was given. The following day, the right eye appeared more inflamed and a cataract had now obstructed the view of the retina. Ultrasonography of the right eye suggested a possible retinal detachment. The visual acuity in his left eye had decreased to 20/30, and a new vitreous inflammatory cell infiltrate was noticed. A pars plana lensectomy and another vitrectomy were performed for the right eye on the fourth day after presentation. At this time, an intravitreal injection of amphotericin B (dose, 10 µg/0.1 mL) was administered in both eyes. Two days later, the vitritis in the right eye persisted and a fourth intravitreal injection of amphotericin B (dose, 5 µg/0.1 mL) was given. One week after presentation, the vitreous haze prevented a view of the retina in the right eye, and there appeared to be a persistent retinal detachment on an ultrasound scan. The patient was thus taken back to the operating room for a third pars plana vitrectomy and another intravitreal injection of amphotericin B (dose, 5 µg/0.1 mL). The right eye finally began improving, and the patient was discharged from the hospital on the twelfth day after presentation.

Some of the residual amphotericin B in the syringes was kept by the surgeon, not for use but for documentation. The second syringe and the third syringe were compared, presumably 5 µg/0.1 mL and 10 µg/0.1 mL, respectively. The syringe containing the 5 µg dose appeared to be more yellow than the syringe with the 10 µg dose. The 2 syringes were sent to a diagnostic laboratory for testing. The concentration of amphotericin B in the second syringe (presumed to be 5 µg/0.1 mL) actually contained 55 µg/0.1 mL. At last follow-up, 3 months after presentation, his visual acuity was correctable to 20/60 OD and 20/20 OS. A chorioretinal scar was present superotemporal to the fovea where the fungal lesion had been.

CASE 3

A 65-year-old man had undergone uneventful extracapsular cataract extraction in the left eye and developed posterior capsule opacification. This opacification was successfully treated with a Nd:YAG laser capsulotomy 4 months after the cataract surgery. However, 1 month later, he be-

gan reporting of decreased vision in his left eye. On examination, his visual acuity was correctable to 20/30, and he was noted to have a white infiltrate in the anterior vitreous. No anterior chamber inflammation was found. The patient was referred to a retina specialist who began treatment with topical steroids for presumed persistent postoperative inflammation. Although intraocular lymphoma was considered, it was felt to be less likely. After the patient's condition did not improve after being treated with topical steroids, he was taken to the operating room for a vitreous biopsy and intravitreal antibiotics because of a concern for chronic postoperative endophthalmitis. Vitreous cytology and cultures were performed, and intravitreal injections of vancomycin (dose, 1 mg) and ceftazidime (dose, 2.25 mg) were given, with uneventful results. Prior to the intravitreal injection of amphotericin B, it was noted that the syringe was "too yellow." The pharmacist was contacted, and the dilution was confirmed. Because the surgeon did not feel comfortable with the color of the medication, he only injected 40% of the initially intended dose. The following morning, the patient had severe ocular pain in the left eye, and there was marked intraocular inflammation. It was then discovered that the requested dosage was 400 µg/0.1 mL of amphotericin B, instead of 4 µg/0.1 mL. By injecting 40% of the intended dose, the patient received 160 µg of amphotericin B. The patient was immediately taken back to the operating room that morning for a washout of the intravitreal antibiotics. He received periorbital and intravitreal injections of steroids and was monitored closely in the hospital for the next 3 days. Six days after surgery, his visual acuity had improved from light perception to 20/200. A fundoscopic examination at that time revealed vitreous debris and fibrin but no retinal detachment. The patient's visual acuity continued to improve slowly, and 2 years later, his vision was correctable to 20/30. The patient had concentrically constricted visual fields on Goldman perimetry, which was later considered to be nonphysiologic on tangent screen testing. An electroretinogram showed normal B-wave amplitudes with delayed implicit times.

COMMENT

The purpose of this study is to warn clinicians that highly concentrated doses of amphotericin B may be recognizable and avoidable. We also sought to document the clinical course and visual acuity outcomes of patients who were treated with highly concentrated intravitreal doses of amphotericin B. The ordering physician and the pharmacy need to be aware of the microgram dosing, as opposed to the milligram dosing, for most agents. In our series of case reports, the treating physician noted that the amphotericin appeared yellow in every case. Every patient developed severe intraocular inflammation and required multiple surgical procedures. Two of our patients subsequently developed retinal detachments, and 2 were left aphakic. The patients' outcomes were surprisingly good, with all 3 patients attaining at least 20/60 visual acuity in the affected eye.

To the best of our knowledge, this is the first report of human patients who were treated with highly concen-

trated doses of amphotericin B from an intravitreal injection. There have only been 2 case reports in which patients received high doses of intracameral amphotericin B.^{10,11} In both cases, the fungi were successfully eradicated, but both patients developed severe toxicity and eventually became blind. Most of the reports on ocular toxicity from amphotericin B come from animal studies.⁸⁻¹³ Axelrod et al⁸ injected various concentrations of commercially available amphotericin B into the vitreous cavities of rabbit eyes. They found that doses of 5 and 10 μg did not cause any changes clinically, microscopically, or electroretinographically when injected into the center of the vitreous cavity. They did find microscopic evidence of retinal necrosis when the amphotericin B was injected forcefully very close to the retina. Doses greater than 25 μg were extremely toxic and caused profound inflammation and retinal detachments. Because amphotericin B alters the permeability of cellular membranes, it was felt that the retinal detachments were partially caused by transudation of fluid into the subretinal space.⁸ Souri and Green⁹ performed similar experiments and found that cataracts were frequently observed at doses greater than 75 μg . They also found microscopic evidence of retinal necrosis with doses as low as 1 μg . Because of these studies, intravitreal injections of amphotericin B of 5 to 10 μg doses have been routinely used to treat fungal endophthalmitis.^{4,5}

In this series of case reports, the physicians were alerted to that fact that the amphotericin B appeared too yellow instead of being almost colorless (suggesting a proper dilution). The **Figure** shows the color differences of 3 different concentrations of amphotericin B. The more concentrated doses appear yellow (ie, the 2 leftmost syringes), and the usual treatment dose appears almost colorless (ie, the rightmost syringe). Physicians should pay close attention to the color of amphotericin B prior to an intravitreal injection, and they should question or discard any solution that appears too yellow. Such attention to the solution will help prevent injections of highly concentrated amphotericin B and its potentially severe consequences. The visual acuity outcome in each of these patients was fairly good at the most recent follow-up; however, every patient required multiple surgical procedures to stabilize the affected eye. We feel that the good outcomes in our patients resulted from promptly taking the patients back to the operating room for a repeat vitrectomy and vitreous washout when the diagnosis of amphotericin toxicity was first suspected.

In 1992, medication errors occurred in 5% of all patients admitted to the hospital.¹⁴ However, this rate had increased dramatically to 24% by 1999.¹⁵ A report by the Institute of Medicine in 1999 estimated that tens of thousands of patients die and hundreds of thousands of patients experience nonfatal injuries each year in the United States as the result of medical errors.¹⁶ The ordering and transcription of prescriptions by physicians has been found to be the source of the medication errors in 50% to 61% of cases.¹⁷⁻¹⁹ The Institute of Medicine has endorsed electronic prescribing as a promising approach for preventing medication errors.²⁰ A large meta-analysis of computerized physician order entry systems showed that 80% of studies reported a significant reduction in the total number of prescribing errors when computerized physi-



Figure. Three separate concentrations of amphotericin B: 500 $\mu\text{g}/0.1$ mL (left syringe), 50 $\mu\text{g}/0.1$ mL (middle syringe), and 5 $\mu\text{g}/0.1$ mL (right syringe).

cians' orders were used instead of handwritten orders.¹⁹ The authors concluded that the existing evidence suggests that computerized physician order entry systems are associated with a significant reduction in prescribing errors. A computerized order entry system was not available for any of the cases in this series. An electronic ordering system would have likely only prevented the dosing error in case 3, in which the incorrect dose was ordered. The error in the other 2 cases occurred during the dilution of the medication. It is important for both the treating physician and the pharmacist to be aware of the microgram dosing of amphotericin B and, more importantly, to know that the amphotericin B solution for intraocular injections should be almost colorless.

In summary, we present 3 cases of intraocular toxicity from highly concentrated amphotericin B in patients presumed to have fungal endophthalmitis. Although the visual acuity outcome for each of our patients was good, subtle retinal damage was likely. Each patient required multiple surgical interventions to stabilize the affected eye. Both cataract formation and retinal detachment were observed in 2 cases. In all 3 cases, the concentrated amphotericin B appeared to be "too yellow." We feel that physicians should carefully observe the color of the solution and be cautious in the dosing of amphotericin B for the treatment of fungal endophthalmitis. If the solution has a yellow color, then the solution should not be injected.

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Ophthalmological Numismatics

One of the best-regarded Venezuelan surgeons of his day, Eliseo Acosta (1819-1879) also performed ophthalmic surgery. Acosta studied in Caracas, London, and Paris before returning home to teach at the Central University of Venezuela, where he was to become Director of the Medical Faculty. He was an early proponent of the use of chloroform anesthesia in surgery. He was honored by the Pan-American Association of Ophthalmology on the occasion of its sixth congress, which was held in Caracas, Venezuela, in 1960.

In 1960, this posthumous medal was issued for the Sixth Pan-American Congress of Ophthalmology to commemorate Acosta. It was struck in silvered bronze and is 45 mm in diameter. The obverse depicts Acosta's clothed bust, three-quarters to the right. The reverse depicts the symbol of the Pan-American Association of Ophthalmology, a map of the western hemisphere. The medal was presented to the attendees of the congress.



Courtesy of: Jay M. Galst, MD, Clinical Associate Professor, New York Medical College; and Peter van Alfen, PhD, Associate Curator, American Numismatic Society.

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