INTRAVITREAL INJECTION OF THERAPEUTIC AGENTS

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Background: Intravitreal injection (IVI) with administration of various pharmacological agents is a mainstay of treatment in ophthalmology for endopthalmitis, viral retinitis, age-related macular degeneration, cystoid macular edema, diabetic retinopathy, uveitis, vascular occlusions, and retinal detachment. The indications and therapeutic agents are reviewed in this study.

Methods: A search of the English, German, and Spanish language MEDLINE database was conducted. A total of 654 references spanning the period through early 2008 were individually evaluated.

Results: The advantage of the IVI technique is the ability to maximize intraocular levels of medications and to avoid the toxicities associated with systemic treatment. Intravitreal injection has been used to deliver several types of pharmacological agents into the vitreous cavity: antiinfective and antiinflammatory medications, immunomodulators, anticancer agents, gas, antivascular endothelial growth factor, and several others. The goal of this review is to provide a detailed description of the properties of numerous therapeutic agents that can be delivered through IVI, potential complications of the technique, and recommendations to avoid side effects.

Conclusion: The IVI technique is a valuable tool that can be tailored to the disease process of interest based on the pharmacological agent selected. This review provides the reader with a comprehensive summary of the IVI technique and its multitude of uses.

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Intravitreal injection (IVI) was initially performed for treatment of retinal detachment (RD) and vitreous hemorrhage. In 1895, Deutschmann[1] injected transplanted rabbit vitreous, and Ohm[2] injected air in the vitreous cavity for the repair of RD. During subsequent decades, the use of IVI was limited to administration of saline[3–7] and air.[8] In the 1960s and 1970s, long-lasting gases were developed for the repair of complex RD.[9] Intravitreal penicillin for treatment of endophthalmitis was attempted in the late 1940s,[10–12] but was subsequently abandoned by the same authors in favor of systemic and subconjunctival injection.

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The modern era of IVI began in the early 1970s with the investigation of the blood ocular barriers.[13,14] The results of these investigations stimulated the use of IVI of antibiotics for treatment of endophthalmitis and steroids for treatment of intraocular inflammation to bypass anatomical barriers in the eye.[15–17] This concept heralded the advent of IVI of antiinflammatory and antineoplastic compounds in the 1970s to 1980s, antivirals in the 1980s to 1990s, triamcinolone acetonide (TA), and vascular endothelial growth factor (VEGF) inhibitors in the 2000s, setting the stage for a paradigm shift in how therapeutic agents are delivered to the eye.[18] Medicare claims data indicated that 325,000 IVIs (CPT 67028) codes had been filed in 2006 alone,[19] and the number is likely in excess of a million today. Intravitreal injection has been used to deliver many types of medications into the vitreous cavity: antiinfective (antibiotic, antifungal, and antiviral), antiinflammatory (nonsteroidal antiinflammatory, steroids, and immunomodulators), anticancer agents, gas, anti-VEGF, etc. With numerous novel therapies currently being investigated in clin-

ical trials, it is likely that the number of drugs under development for IVI will continue to increase.

Intravitreal Injection Technique

The use of preoperative topical antibiotics is not widespread despite evidence that this method can reduce the conjunctival bacterial flora.[20–26] A recent report of a large series of IVI without preoperative use of antibiotics showed a low rate of endophthalmitis, indicating that the preoperative antibiotic may not be needed in each case.[27] Another study involving more than 16,000 patients receiving office-based IVIs of anti-VEGF demonstrated a low rate of endophthalmitis (0.02%) despite variable preoperative prophylaxis.[28]

Intravitreal injection is performed under topical anesthesia, usually in an office-based setting. Clinicians should use aseptic techniques and use povidone–iodine to minimize the conjunctival bacterial flora.[20–24] The type of anesthesia used with IVI varies between retinal specialists. Although 98% of retinal physicians surveyed in 2006 reported the use of anesthesia before IVI, the mode of anesthesia administration was divided between topical anesthesia (66.6%) and subconjunctival (33.3%).[29] Anesthesia is usually accomplished with either cotton-tip applicators soaked in lidocaine or subconjunctival injection of 2% lidocaine or 4% lidocaine jelly. Other options include topical anesthetics (lidocaine, proparacaine, or tetracaine) or the application of tetracaine jelly. Typically, a povidone–iodine (5%) solution is applied to the eye either in solution form or povidone followed by thorough cleaning of the eyelashes, with subsequent application of a lid speculum. The anesthetics used (proparacaine, lidocaine, or bupivacaine) have been shown to be nontoxic to intraocular structures in rabbits. Intraocular application of lidocaine up to 2%, bupivacaine up to 0.75%, and a combination of the two anesthetics induced reversible electroretinogram changes in the rabbit retina but did not result in any adverse clinical reactions or histologic retinal abnormalities.[30]

After anesthesia, the pharmacological agent for IVI (either prepared by the manufacturer, such as ranibizumab, or prepared by the compounding pharmacist, such as bevacizumab) is drawn into a 1-mL tuberculin syringe from a sterile bottle, usually with a filter needle in place for the IVI itself. Thirty- to 32-gauge needles are most commonly used, whereas larger bore needles (27 or 28.5 gauge) are less frequently used.[31]

The injection site is usually the infero-temporal quadrant to avoid drug deposition in front of the visual axis. The pars plana is 3 mm to 4 mm posterior to the limbus. The needle should be aimed at the midvitreous with the bevel upward, and the injection should be done slowly to avoid jet formation or cavitary flow. The needle should not be introduced all the way to the hub. Using a single smooth continuous maneuver, the pharmacological agent is injected into the eye. The volume of the administered compound is relatively consistent between studies, with the most commonly used volume being 50 μL to 100 μL. However, the studies using standard volumes do not account for the reduction in size of the human vitreous that occurs with age.[32] Generally, most clinicians believe that 100 μL is the largest safe volume, and larger volumes are reserved mainly for administration of gas for pneumatic retinopexy (PR).[31,33] The needle is removed simultaneously with the application of a cotton-tipped applicator over the sclerotomy site to minimize reflux of material (particularly if the injected volume exceeded 0.05 mL).

The use of postoperative antibiotics is routine, reported in approximately 59% of the studies.[31] A postinjection course of topical antibiotics typically lasts for 3 days to 7 days.

Delivery of Antiinfective Agents

Antibacterial Drugs

Administration of antibiotics directly into the vitreous body through IVI is the standard of care for the treatment of bacterial endophthalmitis. Table 1 shows the recommended dosage of antibiotic for IVI, the half-life of each antibiotic in the vitreous body, and the maximum nontoxic dosage for IVI. Selection of an appropriate antibiotic depends on prevailing organisms in the geographic area, mechanism of endophthalmitis, strain of bacteria, sensitivity and resistance, as well as patient factors (e.g., allergies and sensitivities). In the setting of acute postsurgical endophthalmitis, vancomycin in combination with either a third-generation cephalosporin or amikacin is typically injected as initial empirical therapy.

Aminoglycosides. Aminoglycosides have potent activity against gram-negative bacteria but are limited by their potential toxicity. The aminoglycoside antibiotic family—streptomycin, gentamicin, kanamycin, tobramycin, amikacin, and netilmicin—has a chemical composition of an organic base with amino sugars and are synthesized from numerous species of fungal organisms. Their wide spectrum of antibiotic activity against both gram-positive and gram-negative bacteria is due to the ability to interfere with synthesis of ribosomal proteins. Amikacin is often the aminoglycoside of choice for human endophthalmitis,[18] whereas gentamicin and clindamycin were shown to be effective in the prevention of

Table 1. Recommended Dose and Pharmacologic Profile of Intravitreal Antibiotics

Antibiotic	Intravitreal Dose (mg)	Vitreous Half-Life (h)
Aminoglycosides		
Amikacin	0.4	24
Gentamicin	0.2	12–35
Kanamycin		
Netilmicin	0.25	24
Streptomycin		
Tobramycin	0.2	16
Penicillins		
Ampicillin	5	6
Azlocillin		
Carbenicillin	0.5–2	10–20
Cloxacillin		
Dicloxacillin		
Methicillin	2	3–5
Mezlocillin		
Oxacillin	0.5	
Penicillin G	0.2–0.3	3
Piperacillin	1.5	
Ticarcillin	3	
Cephalosporins		
Cefamandole	0.08	0.5
Cefazolin	0.5–2.0	7
Cefotaxime	0.4	
Cefotetan	1	
Cefoxitin		
Ceftazidime	2	16
Ceftriaxone	2	12
Cephalexin		3
Cephaloridine	2.5	
Cephalothin	2	2.4
Moxolactam	1.25–2.0	20
Fluoroquinolones		
Ciprofloxacin	0.1	5
Garenoxacin	0.1–2	
Gatifloxacin	0.4	
Levofloxacin	0.625	
Moxifloxacin	0.05–0.16	1.72
Norfloxacin		
Ofloxacin	0.05	5.65
Pefloxacin	0.2	3
Travofloxacin	0.025	
Macrolides		
Erythromycin	0.5	30
Clarithromycin	1	2
Lincosamides		
Lincomycin	1	7–8
Clindamycin	0.5–1	
Carbapenems		
Imipenem	0.5	
Meropenem		
Glycopeptides		
Vancomycin	1	30
Teicoplanin	0.75	
Miscellaneous		
Aztreonam	0.1	7.5
Chloramphenicol	2	10
Cotrimoxazole	1.6	
Doxycycline	0.125	
Chloramphenicol	1	

Table 1.

Antibiotic	Intravitreal Dose (mg)	Vitreous Half-Life (h)
Antifungals		
Polyene antimycotics		
Amphotericin B	0.005–0.01	6.9–15.1
Natamycin	3 X 0.025	
Nystatin	200 U	
Azoles		
Fluconazole	0.1	3.1
Itraconazole	0.01	
Ketoconazole	0.54	
Miconazole	0.025–0.05	2
Oxiconazole	0.1	
Terconazole	10	
Voriconazole	0.05–0.1	2.5
Echinocandins		
Caspofungin	0.1	
Miscellaneous		
Faeriefungin	0.1	
Flucytosine	0.1	
Cilofungin	0.32	

acute posttraumatic bacterial endophthalmitis.[34,35] Side effects of parenteral aminoglycosides include ototoxicity and neprotoxicity.[18]

Toxicity of intravitreal aminoglycosides, which can occur with doses as low as 10 μg to 200 μg of gentamicin, includes the following: 1) formation of lysosomal cellular inclusions, resulting in ocular cell toxicity and loss of function; 2) cataracts following a dose greater than 200 μg of gentamicin; and 3) retinal infarction due to gentamicin and tobramycin.[36,37] For this reason, some advocate the use of low-dose gentamicin (4–8 μg) in the infusion fluid.[34,35] Current recommendations emphasize administration of IVI into the anterior vitreous with the needle bevel facing the lens, slow injection of the medication, and avoidance of repeated IVI in short intervals (less than 1 week, except for the negative sensitivity results for the antibiotic used), especially in combination at low doses with vancomycin or clindamycin to limit the possibility of toxicity.[18,34]

Cephalosporin. The third-generation cephalosporins, which include ceftriaxone, ceftazidime, and moxolactam, are a mainstay in the initial management of IVI. They have increased activity against gram-negative organisms but are less active against gram-positive organisms.[38] The cephalosporins were first isolated from the fungus *Cephalosporium acremonium.* These semisynthetic antibiotics have a similar chemical structure and mechanism of action to the penicillin family. The first generation of cephalosporins, which includes cefazolin, cephalexin, and cephalothin, has a wide spectrum of activity against gram-positive bac-

teria and some activity against gram-negative bacteria. The second generation, represented by cefotetan, cefoxitin, and cefamandole, has more activity against gram-negative organisms but are less active against gram-positive bacteria, especially *Staphylococcus*. Other members of this family—cephaloridine, cephalothin, ceftazidime, and cefotaxime—have demonstrated efficacy and safety in experimental models of progression of endophthalmitis without toxicity to intraocular structures in rabbit eyes.[39–44] Cefazolin is currently not recommended for treatment of endophthalmitis due to increase in resistant organisms.[39,42] Intravitreal injection of moxalactam inhibited experimental *Staphylococcus aureus* endophthalmitis but resulted in retinal abnormalities in rabbits at doses of 2.5 mg or higher.[45,46]

Glycopeptides

Vancomycin.—Vancomycin is the preeminent choice for initial treatment of acute postoperative endophthalmitis due to gram-positive organisms. Vancomycin is an antibiotic produced by *Streptomyces asianis* and has a unique chemical structure that lends it high activity against gram-positive cocci.[47] Vancomycin inhibits bacterial cell wall synthesis. Vancomycin, first developed in 1958, has become an extremely effective drug in treatment of severe gram-positive ocular infections (keratitis, endophthalmitis, orbital cellulitis) in the setting of antibiotic-resistant bacteria or antibiotic allergy. However, in recent years, a controversy arose over the use of this agent in ophthalmology, especially as a prophylaxis in elective cataract surgery.[18] The identification of vancomycin resistance in coagulase-negative *Staphylococci* in 1987, followed by cases of resistant *Enterococci* in 1988, has led to calls for the judicious use of this agent in ophthalmology.[48,49]

Intravitreal vancomycin is the drug of choice for endophthalmitis caused by gram-positive organisms.[18] Intravitreal injection of vancomycin was nontoxic to ocular structures in the clinically recommended dose of 1 mg/0.1 mL; added to infusion fluid for intraocular surgery, the nontoxic dose is 8 mg/mL to 32 mg/mL.[50] A dose of 1 mg/0.1 mL halted progression of methicillin-resistant *S. aureus* endophthalmitis.[47] We urge caution in patients with silicone oil, because nontoxic concentrations of this drug may become toxic after IVI in postvitrectomy, silicone-filled rabbit eyes.[51] The threshold for ocular toxicity in rabbits decreased to one quarter of the nontoxic dosage in an unoperated eye compared with silicone-filled eyes.[51] In the Endophthalmitis Vitrectomy Study,[52] all gram-positive bacteria including methicillin-resistant *S. aureus* were susceptible to vancomycin.[53]

In cases of endophthalmitis due to gram-positive organisms, resistance to vancomycin is still rare, at only 2.1% of a reported 8,500 strains of bacteria.[54] However, ophthalmologists should use caution when using vancomycin, because the incidence of vancomycin-resistant *S. aureus* and *Enterococci* isolates continues to rise.[49] New antibiotics such as quinupristin-dalfopristin, linezolid, and daptomycin may show promise in the treatment of vancomycin-resistant infections.[55–65] Vancomycin showed synergism with aminoglycoside antibiotics against various organisms, especially *Enterococcus*, and with β-lactams against gram-positive bacteria and some gram-negative bacteria.[54,55]

Teicoplanin.—Teicoplanin is a relatively new glycopeptide antibiotic that is isolated from *Actinoplanes teichomyceticus*. It is active against most gram-positive bacteria, especially *Staphylococci*. Teicoplanin in combination with gentamicin is effective against *Enterococci*. Intravitreal injection of teicoplanin is nontoxic in rabbit retinas at doses up to 750 g/0.1 mL.[66,67]

Penicillins. The penicillins are rarely used for treatment of endophthalmitis because of widespread resistance. Penicillins are a group of antibiotics derived from 6-aminopenicillic acid. They work by inhibiting bacterial cell wall synthesis. Intravitreal injection administration is currently reserved for methicillin, cloxacillin, dicloxacillin, and ampicillin. Methicillin, oxacillin, and ampicillin are penicillinase-resistant, semisynthetic penicillins that can be delivered by IVI and do not cause toxicity at recommended dosages.[68–70] The number of *Staphylococci* species resistant to methicillin and other penicillinase-resistant penicillins has increased.[18] The toxicity, clearance, and efficacy of IVI cloxacillin and dicloxacillin for endophthalmitis management have not been studied.[18]

Extended-spectrum penicillins are alphacarboxypenicillins (e.g., carbenicillin and ticarcillin) and acylaminopenicillins (e.g., azlocillin, mezlocillin, and piperacillin). Although these antibiotics are effective against gram-negative aerobic organisms that cause endophthalmitis, such as *Enterobacteriaceae* and *Pseudomonas*, which are currently resistant to many penicillins, their use is not widespread. Similarly, experimental evidence suggests that intravitreal piperacillin/tazobactam, carbenicillin, ticarcillin, and piperacillin have demonstrated efficacy and lack of toxicity in experimental models.[71–73]

Fluoroquinolones. The fluoroquinolones are not widely used via IVI for treatment of endophthalmitis. The fluoroquinolones are derived from nalidixic acid and have a potent activity against gram-negative bacteria. Ciprofloxacin is considered effective for prophylaxis and treatment of intraocular infections[74] and is not toxic to the rabbit retina.[75]

Norfloxacin, ofloxacin, and pefloxacin are only administered orally for prevention or management of endophthalmitis[76] but have not been used for IVI. Despite their initial efficacy, resistance to first- and second-generation quinolones in bacterial keratitis and other ophthalmologic infections is increasing.[76,77] This prompted the development of third- (levofloxacin) and fourth-generation quinolones (gatifloxacin, garenonoxacin, and moxifloxacin) during the past decade. New quinolones achieved an increased efficacy against gram-positive organisms while maintaining activity against gram-negative bacteria.[78–80]

The third- and fourth-generation fluoroquinolones represent a good first-line antibiotic treatment for many ocular infections. Intravitreal injection of these antibiotics did not result in electroretinographic changes or retinal toxicity in rabbits when administered in doses up to 625 μg for levofloxacin,[78] 400 μg for gatifloxacin,[78] 4,000 μg for garenonoxacin,[79] and 160 μg for moxifloxacin.[80]

Macrolides. Due to increasing resistance, erythromycin has rarely been used for IVI therapy of endophthalmitis. Erythromycin, which was first synthesized from *Streptomyces erytheus* in 1952, has activity against gram-positive cocci and *Neisseria* species. Its mechanism of action is inhibition of protein synthesis by binding the 23S rRNA molecule of the 50S subunit of bacterial ribosome, inhibiting peptide growth.[81] Despite effectiveness against experimental *S. aureus* endophthalmitis and a lack of ocular toxicity,[82] erythromycin is not used due to widespread resistance. Intravitreal clarithromycin was also nontoxic to rabbit eyes in a dose of up to 1.0 mg.[83]

Lincosamides. The lincosamides are rarely used for IVI therapy of endophthalmitis.

Lincomycin.—Lincomycin is derived from the actinomycete *Streptomyces lincolnensis* and has a mechanism of action similar to that of erythromycin.[81,84] It is effective against Group A *Streptococci*, *Pneumococci*, penicillinase-producing *S. aureus*, *Corynebacteria*, *Clostridia*, and *Bacteroides* species.

Clindamycin.—Clindamycin, a semisynthetic derivative of lincomycin, has the same antibiotic activity and mechanism of action as lincomycin but with higher potency.[18] Intravitreal injection of clindamycin has demonstrated efficacy for prophylaxis against endophthalmitis and is nontoxic to the retina.[34,68] Intravitreal injection or intracameral injection of clindamycin (45 μg) in conjunction with IVI or intracameral gentamicin (40 μg) was superior to balanced salt solution IVI/intracameral injections in the prevention of endophthalmitis after penetrating eye injury (2.3% vs. 0.3%, $P = 0.04$).[34] Additionally, it was found that IVI antibiotic administration was superior to intracameral administration.[34] These data strongly suggested that intraocular and especially intravitreal gentamicin and clindamycin were effective in preventing acute posttraumatic bacterial endophthalmitis. Intravitreal injection of 1.0 mg clindamycin in 0.1 mL and 1.0 mg of dexamethasone in 0.1 mL was also well tolerated in patients with toxoplasmic retinochoroiditis.[85] This treatment resulted in a favorable response after 2 weeks; specifically, there was improvement in visual acuity and preservation of the disk and macula, suggesting that this regimen may be an additional tool in treatment of toxoplasmic retinochoroiditis.[85] Further research into IVI clindamycin is warranted because the reported adverse drug reaction rate to clindamycin for ocular toxoplasmosis is 22.5%.[86]

Carbapenems. Imipenem/cilastatin is a combination of two antibiotics, cilastatin and the β-lactam theinamycin, and works by inhibiting cell wall synthesis. It has a wide spectrum of activity against gram-positive and gram-negative aerobic and anaerobic bacteria. Systemic imipenem has good ocular penetration, with aqueous concentration of 2.99 μg/mL and vitreous concentration of 2.53 μg/mL 2 hours after administration of 1 g of imipenem in 25 patients undergoing routine cataract extraction.[87] Although rarely used in IVI therapy, imipenem has demonstrated efficacy in one case of *Pseudomonas* endophthalmitis and was nontoxic to ocular structures.[88] Experimental IVI of imipenem for treatment of experimental *Bacillus cereus* and *Pseudomonas* endophthalmitis in pigs demonstrated safety and efficacy.[89,90] The combination of amikacin and vancomycin was superior to IVI of imipenem for treatment of experimental *S. aureus* endophthalmitis in rabbits.[91]

Chloramphenicol. Chloramphenicol is an antibiotic first isolated from *Streptomyces venezuelae* in 1947.[18] It has a wide spectrum of action that includes many gram-positive and gram-negative baceria but excludes *P. aeruginosa*.[18] Systemic use of this antibiotic should be carefully monitored, because it may result in serious toxic reactions such as fatal blood dyscrasias.[92] Intravitreal injection of chloramphenicol (1 mg), in contrast, is nontoxic to all intraocular structures and is effective against experimental endophthalmitis.[93] The lack of coverage of *P. aeruginosa* has limited the use of IVI chloramphenicol for treatment of endophthalmitis.[18]

Antifungal Agents

Fungal endophthalmitis, representing only 3% to 13% of all reported cases of endophthalmitis, can be a difficult diagnosis due to the long onset of symptoms and the prolonged time necessary for organism iden-

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