Intravitreal Injections: Technique and Infection Prophylaxis

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Intravitreal injections have become a mainstay of medical therapy for the management of retinal diseases. As an office-based procedure, this modality is rapidly replacing laser photocoagulation as the most common. The efficacy of the injected medications coupled with the relative ease of performing these procedures makes them both appealing and practical for the patient and doctor alike. The efficiency and simplicity of the procedure, however, should not preclude a careful, consistent protocol, and proper aseptic technique.

Today, the armamentarium of intravitreal medications includes triamcinolone acetonide (Kenalog; Bristol Myers Squibb, New York, NY), pegaptanib (Macugen; OSI/Eyetech and Pfizer, New York, NY), bevacizumab (Avastin; Genentech, San Fancisco); and ranibizumab (Lucentis; Genentech), as well as numerous other agents available on an investigational basis such as VEGF trap (Regeneron; Tarrytown, NY). In addition to exudative macular degeneration, intravitreal injections are being used to treat proliferative diabetic retinopathy, diabetic macular edema, and cystoid macular edema from various etiologies including branch and central retina vein occlusions. As more agents become available and the indications for intravitreal medical therapy expand, the number of procedures performed per year will rise exponentially.

Although an intravitreal injection is an extremely safe procedure, it is not completely devoid of risk. These risks can include vitreous hemorrhage, retinal tear, and retinal detachment, as well as endophthtalmitis, which is perhaps the physician's most feared complication. Endophthalmitis following intravitreal injection has been reported to occur at a rate of 1 per 1,000 procedures (0.1%),[1] which is similar to the rates reported for postoperative endophthalmitis following phacoemulsification surgery. However, given the fact that most patients will receive multiple injections over time, sometimes even in both eyes, the "per patient" risk is even greater. Therefore, the importance of adequate infection prophylaxis is an ever-increasing concern.

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RISK ASSESSMENT

Once it has been determined that a patient may benefit from an intravitreal injection, an infection risk assessment must be performed. This second part of the equation is as important as the first. Avoiding harm to the patient is arguably as important as treating the pathological process with which a patient presents. An infection risk "checklist" should address the following questions:

- Is there active blepharitis in either eye?
- Is the patient able to cooperate during the injection procedure and not interfere with sterile technique?
- Will the patient be able to use or receive antibiotic drops during the post-injection period?
- Will the patient be able to recognize symptoms of endophthalmitis in a timely fashion should they develop?

- Is the patient likely to return for follow-up appointments?

Active blepharitis is a definite contraindication to intravitreal injection. If blepharitis is present, it is prudent to treat this condition with lid scrubs and topical antibiotic drops or ointment until it is resolved prior to performing the procedure. If the patient is unable to cooperate with sterile technique, use antibiotic drops post-procedure, promptly recognize the signs and symptoms of endophthalmitis or return for follow-up visits, then an alternative therapy should be considered.

TECHNIQUE

The protocol for intravitreal injections of medications has evolved over the last few years. Proper technique has made this procedure one that is remarkably well tolerated by patients. Regardless of the agent being injected, proper anesthesia is an essential step toward this end. This can be accomplished with injection of subconjunctival 2% lidocaine at the injection site or with topical xylocaine jelly. Subsequently, the lids and periocular area should be prepped with 5% povidone/iodine with a drop in the cul de sac. Draping is optional, though this step is becoming less common among retina specialists, as is gloving. The injection is most commonly given inferotemporally because of ease of access, 3.5- to 4-mm posterior to the limbus through pars plana. Visualization of the fundus via indirect ophthalmoscopy should then be performed to ensure that no complications have occurred, and that the retina and optic nerve head are perfused.

Intraocular pressure check by applanation tonometry is not necessary if the nerve appears perfused. Following the procedure, patients should use topical antibiotics for at least 3 days, and it is advisable to instruct patients to begin using the antibiotic drops 2 days prior to the procedure.

ANTIBIOTIC SELECTION

A major strategy in preventing postoperative infection following intravitreal injections involves the proper selection of antibiotics. There are four main characteristics that one should evaluate in an ocular antibiotic prior to making a selection. First, the drug must be able to effectively penetrate into the intraocular tissues. Second, the drug must be of adequate potency, which, in the case of antibiotics, is measured by the mean inhibitory concentration (MIC). Third, there must be minimal bacterial resistance to the drug. Finally, the drug should be able to rapidly eradicate bacteria, before infection is able to set in.

The fluoroquinolone class is currently the mainstay of therapy in the perioperative period for patients receiving intravitreal injections. Among the third-generation fluoroquinolones (ofloaxacin, ciprofloxacin, and levofloaxacin) ofloxacin has been shown to reduce the incidence of endophthalmitis in cataract surgery patients better than ciprofloxacin,[2] most likely due to the superior anterior chamber penetration of ofloxacin.[3]

The fourth-generation fluoroquinolones (gatifloxacin and moxifloxacin) represent a vast improvement over their predecessors in terms of efficacy and bacterial resistance. Kowalski and colleagues determined that gatifloxacin and moxifloxacin had greater in vitro antibacterial activity than any third-generation fluoroquinolone.[4] Furthermore, there are significantly fewer resistant isolates of coagulase negative *Staphylococcus* and *S aureus* to the fourth-generation fluoroquinolones than to the third-generation agents.[5] In vitro data also suggests that the fourth generation fluoroquinolones achieve the same penetration standards set by the third generations', with concentration levels exceeding the MICs of key gram positive pathogens such as *S epidermidis*, *S aureus* and *Streptococcus pneumoniae.*

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In a recent study, De Castro et al examined the efficacy of gatifloxacin in a rabbit model of endophthalmitis.[6] *S aureus* recovery from the aqueous and vitreous humor was much less common in animals that received gatifloxacin than in the control group. These studies have held great promise for fourth-generation fluoroquinolones as antiinfectives, and clinical studies are being performed to investigate their potential efficacy in humans.

When comparing the commercially available fourth generation agents against each other, it is interesting to note that the MIC 90 in vitro data differs from that obtained from molecule to molecule comparisons of gatifloxacin to moxifloxacin. From a molecule to molecule standpoint, moxifloxacin appears to be a more potent antibacterial agent against *S aureus*, *S epidermidis*, *S pneumoniae,* and *S pyogenes*. However, commercially available gatifloxacin (Zymar; Allergan, Irvine, CA) appears to be a more potent bacteriostatic agent than moxifloxacin (Vigamox; Alcon, Fort Worth, TX) against these microbes as well as methicillin-resistant *S aureus* (MRSA), key gram-negative bacteria such as *Klebsiella pneumoniae* and *Enterobacter aerogenes*, and atypical organisms such as *Nocardia asteroides*, *Mycobaterium chelonae* and *M fortuitum*.[7] The substantially lower MIC values associated with commercially available Zymar 0.3% may be related to the fact that it is preserved with 0.005% benzalkonium chloride.

Finally, "speed of kill" is also an important consideration when selecting an antibiotic to be used after an intravitreal injection. In vitro data suggests that Zymar produces more rapid and complete killing of Staphylococcus bacteria,[8] MRSA, *Haemophilus influenzae* and *S pneumoniae*[9] when compared to Vigamox. Whether or not the in vitro data translates into clinical fact in humans is yet to be determined.

CONCLUSION

In summary, intravitreal medications can very effectively treat certain posterior segment diseases. Careful technique and adequate patient screening and monitoring can help to significantly reduce procedure-related complications. Perioperative use of fourth generation fluoroquinolone antiinfectives can aid in reducing the complications ascribed to bacterial infection. ■

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