Intracameral antibiotic prophylaxis

New product approved to prevent postoperative endophthalmitis following cataract surgery
Introduction

Endophthalmitis is a severely damaging condition involving intraocular inflammation of the vitreous cavity and the anterior chamber as a result of infection of the eye. This issue can arise post-cataract surgery and can have detrimental effects on the visual outcome of the patient.

It is current standard practice to prevent endophthalmitis through prophylactic treatment. Until now there has been no approved commercial product available to combat this problem even though 'off-label' use products have been employed. However, the use of 'off-label' products gives rise to uncertainty and security issues for practitioners and patients alike.

Therefore, during the XXX Congress of the European Society of Cataract and Refractive Surgeons in Milan, Italy, Laboratoires Théa held a symposium dedicated to the topic of antibiotic prophylaxis for endophthalmitis following cataract surgery.

Co-chairing this symposium, alongside Professor Anders Behndig, was Professor Peter Barry (President of the European Society of Cataract and Refractive Surgeons, and Consultant Ophthalmologist at the Royal Victoria Eye and Ear Hospital and St Vincent’s University Hospital, Dublin, Ireland) who has been integral in the development of research into intracameral antibiotics for the prevention of endophthalmitis after cataract surgery. Prof. Barry explained, “As chairman of the ESCRS endophthalmitis study group,1 we had three objectives: the first was to prove in a clinical trial the efficacy of treatment, and we have achieved that; the second was to encourage industry to come up with an approved commercial product to overcome the risk of lower security of using a non-approved product; and the third objective, if we can achieve the second one, is to identify and create a European endophthalmitis registry. We hope that this registry will be ready for Amsterdam next year.”

With the requirements of the industry in mind, Laboratoires Théa has introduced a cefuroxime preparation for intracameral use that has been approved for use as antibiotic prophylaxis of postoperative endophthalmitis following cataract surgery. This new product was highlighted during the symposium and in this supplement OTEurope will discuss the outcomes of this meeting and the potential benefits this novel product could bring to the ophthalmology community.
Endophthalmitis and cataract surgery

“Endophthalmitis is intraocular inflammation that involves the vitreous cavity and the anterior chamber as a result of invasion of the eye by microorganisms,” said Professor Jorge Alió (Professor & Chairman of Ophthalmology, Universidad Miguel Hernández, VISSUM Instituto Oftalmológico de Alicante, Spain). There are two types of endophthalmitis, endogenous — pertaining to the spread of bacteria from an internal source — and exogenous — resulting from the introduction of an external bacterial source during or immediately following ocular surgery.

The source of endophthalmitis is usually contamination of the eye by bacteria from commensal flora of the ocular surface. This contamination can occur during surgery or immediately after surgery. As a result of the high frequency of cataract procedures performed this makes it more likely that incidences of this infectious condition will be experienced post-cataract surgery.

“The amount of infection depends on the bacterial load and any impairment to the immune privilege of the eye,” said Prof. Alió. “This infection causes inflammation, which is truly destructive and affects the posterior segment. There are bacterial toxins, proteases and an intense inflammatory response from the host that affects the retina, the choroidal and the retinal vessels as well as the anterior segment structures creating a tremendous problem for the patient in terms of outcomes.”

Figures estimate that the postoperative incidence of endophthalmitis ranges from 0.03–0.15% worldwide. This is indeed a problem that has a diverse representation depending on the part of the world, so you have different numbers of incidences depending on the area,” said Prof. Alió. “This is a problem that affects a large number of people if you consider that cataract surgery is the most frequently performed surgical procedure.”

In agreement with this Professor Anders Behndig (Professor at the Department of Clinical Sciences/Ophthalmology, Umeå University Hospital, Umeå, Sweden) said, “Cataract surgery is a very special surgical procedure, so it is in every case an implantation procedure, so we actually use an implant in the eye, which probably increases the risk of infection compared to other types of surgery. Also, we know there is a high risk of intraocular contamination of bacteria from the ocular surface... and we do a very high number of procedures.” So, he noted that even if there is a low frequency of patients contracting endophthalmitis there will still be quite a large volume in absolute numbers.

Additionally, the high expectations of patients for perfect results following cataract surgery compounds the issues surrounding exogenous endophthalmitis infection. “Everybody knows that a cataract surgical procedure is very simple and fast and that the results are always perfect, so there are very high demands from the patients on us to have perfect results every time,” continued Prof. Behndig. “This is a serious threat to the image of cataract surgery because the effect of endophthalmitis is very dramatic and results in a high risk of significant visual loss.”

Visual outcomes
In looking at the Endophthalmitis Vitrectomy Study (EVS), Prof. Alió remarked that the outcomes of patients infected with endophthalmitis are poor even after treatment. “If you look at the EVS, which is one of the most remarkable studies ever performed on surgical endophthalmitis cases, at final follow up visit 5% of patients had no light perception, 53% had less than 20/40 and 74% had less than 20/100,” he continued. “This means that you have poor vision in spite of vitrectomy and in spite of the ophthalmologists’ efforts and in spite of the antibiotic therapy.”

Therefore, although the EVS indicates that endophthalmitis can be treated and cured, the visual outcome of that patient will never be as anticipated and in fact severe visual loss is a typical outcome. “So, the best treatment is not treatment, it is prophylaxis,” asserted Prof. Alió.

Prevention is best practice
“Prevention is indeed the best management of this severe, destructive complication of cataract surgery,” said Prof. Alió. “We can avoid and prevent this infection by avoiding the risk factors and with adequate proactive prophylactic treatment given to the patient proactively in order to avoid the infection.”

“...the effect of endophthalmitis is very dramatic and results in a high risk of significant visual loss.”
Prof. Anders Behndig

Agreeing with this, Prof. Behndig highlighted his findings from the Swedish National Registry. “We have also identified some high-risk groups. High age, for various reasons means increased risk by a factor of 1.7. IOL materials, there is slight risk in reduction in risk with hydrophobic acrylic IOLs, but this is just barely significant. A surgical procedure other than phaco and IOL, such as combined procedures, also means a higher risk. Of course if you do larger procedures it takes more time, which increases the risk,” he said.

Additionally, posterior capsule rupture was discussed, which can pose a highly significant risk. “There has been a discussion about whether you could use intracameral cefuroxime with posterior capsule rupture. We use cefuroxime in all such cases in Sweden and still you see an increased frequency of endophthalmitis, but it’s important to emphasize that these figures would likely be even higher if we did not use intracameral cefuroxime in these cases,” Prof. Behndig added. “There is a small percentage of patients in Sweden that do not receive intracameral antibiotics as some doctors feel it might be dangerous in cases of suspected allergies. If we compare these to the ones who receive intracameral antibiotics, the risk of endophthalmitis is increased by a factor of about 8 for patients who do not receive antibiotics.”

The approaches for the prevention of postoperative endophthalmitis following cataract surgery have been well documented during the past decade. In a review of the literature two approaches have been shown to provide efficient prevention of endophthalmitis. These are antisepsis with povidone-iodine solution into the conjunctiva before surgery and intracameral cefuroxime injection immediately following cataract surgery.
The Swedish experience

Since 1998, all cases of suspected endophthalmitis have been reported to the National Cataract Register in Sweden. With a large number of reporting clinics this register offers a reliable source of data on the incidence and efficacy of preventative measures against endophthalmitis.

“There are different types of endophthalmitis,” said Prof. Behndig. “The ones we fear most and the ones we see most often are the acute forms with symptoms occurring within a week after surgery. It is in these cases that we suspect the bacteria enters the eye during surgery or immediately after surgery, so this is where an antibiotic prophylaxis can have an effect.”

In Sweden the prevalence of endophthalmitis between the years 1998 and 2010 has decreased from over 0.1% to less than 0.02% (Figure 1). However, Prof. Behndig noted that even though intracameral cefuroxime has had an impressive impact on the incidence rate of endophthalmitis it is not the only reason for the reduction. “There has been a gradual reduction in the frequency of endophthalmitis so intracameral cefuroxime is not the whole answer,” he said. “We are also more proficient at performing surgery now, the surgical time has decreased and our patients are slightly younger than those of 10 years ago. So, there are other factors contributing to the gradually lowering frequency of endophthalmitis but the big thing for us has been the introduction of intracameral cefuroxime.”

The 18-year review has shown that there has been a positive trend in the decline of endophthalmitis incidences following cataract surgery in Sweden. “Now, the figures are so low in Sweden that we cannot really see trends of increasing or decreasing incidences unless we pool data over several years,” revealed Prof. Behndig. “So, this is the case now that we almost never see cases of endophthalmitis and it should be remembered that we are talking about approximately 90000 cataract procedures yearly.”

“Often endophthalmitis can be handled successfully,” he continued. “Sometimes the outcome is quite good but how many cases lose their sight because of endophthalmitis? Well this was 1 in 6000 procedures between 2001 and 2004 and between 2005 and 2008 it was down to 1 in 8000 procedures in Sweden, and these are very encouraging figures. And like I said before this decrease is probably due to a decrease in risks factors and surgical complications.”

As a result of this registry in Sweden there has been further work performed by the ESCRS to evaluate various prophylaxis modalities and intracameral cefuroxime is now proposed as a European standard of care.

Figure 1: Incidence of confirmed endophthalmitis after cataract surgery in Sweden, 1998–2010.
Antibiotic prophylaxis: Intracameral cefuroxime

Antibiotic prophylaxis is one part of the preventive measures that should be taken against endophthalmitis infection noted Prof. Behndig. "It's important also to emphasize that prevention measures against endophthalmitis should include pre-op routines with antisepsis, povidone iodine or as we use in Sweden, chlorhexidine, it’s absolutely mandatory to use pre-op draping and as a part of this whole concept antibiotic prophylaxis comes into the picture too and there are also post-op routines that need to be followed. Antibiotic prophylaxis cannot replace anything else that we do to prevent endophthalmitis, but it’s rather an important piece in this puzzle," he said.

"Topical antibiotics can be used during the pre-op and indeed play a role," according to Prof. Alió. However, pre-op antibiotics are not clinically proven to be effective at preventing endophthalmitis. This is a point of controversy, as one audience member highlighted because there is a necessity and ethical obligation to avoid the use of antibiotics so as to not exacerbate bacterial resistance. However, in Prof. Alió’s opinion there is an argument that these should be used as they are effective at decreasing the conjunctival flora, which is the main source of contamination.

Intraoperatively there are extremely efficient antiseptics that can be used. Prof. Alió said, "5% povidone iodine is the most important prophylaxis in the periorbital as it decreases conjunctival and periorbital skin flora." He agreed with Prof. Behndig that draping is necessary and single use instruments are preferred.

"One of the most current measures to take during surgery is the use of intracameral antibiotics, which are becoming the standard of care," added Prof. Alió. This was affirmed with the results of the ESCRs study co-authored by Prof. Barry, which demonstrated the decrease in endophthalmitis risk by 5-fold with the use of intracameral injection of cefuroxime as antibiotic prophylaxis at the end of surgery (Table 1).

In a recent survey conducted by the ESCRs it has been revealed that the majority of ophthalmologists across 33 different countries would use cefuroxime as antibiotic prophylaxis. "74% are always/usually IC antibiotics users. Among those using IC antibiotics, 82% used Cefuroxime (Figure 2). 73% say they would always or almost always use a commercial preparation of intracameral Cefuroxime. If this stated intention were to become reality, this would represent a substantial increase in use (Figure 3); but that doesn’t mean the other said no as...
some of those are using a preparation made by a pharmacy and will continue to do so for economical reasons,” revealed Prof. Barry. “So when you actually boil it down, a mere 8% of those interviewed said that they would not use intracameral cefuroxime virtually under any circumstances, which is very small.\" In 2010, 10-year comparative study results were published on the effectiveness of intracameral cefuroxime in the prevention of post-cataract surgery endophthalmitis in Spain.\(^1\) The results confirmed those found in the ESCRS Study\(^3\) and the Swedish National Cataract Register,\(^4\) that intracameral cefuroxime was effective in reducing the risk of endophthalmitis immediately following cataract surgery. (Please see Table 2 for a list of prospective and retrospective studies.)\(^11,14–19\)

\"An important cohort of patients were evaluated before and after the introduction of intracameral cefuroxime,\" said Prof. Alió. \"Without cefuroxime the incidence of endophthalmitis was found to be 0.59%. This figure was decreased to 0.043% after the introduction of intracameral cefuroxime, demonstrating the extreme effectiveness of this procedure. So, from the evidence-based literature, if you do not use cefuroxime you have a definite risk of more frequent occurrences of endophthalmitis.\"

### Goal of prophylaxis

\"The goal of any kind of prophylaxis is to provide minimal risk of infection with no eye toxicity and no selection of resistance and not too strong antibiotic, we should keep munitions for treatment of potential post-op infections,\" said Professor Beatrice Cochener (President of the SFO and Professor in Ophthalmology at the University of Brest, Brest, France).

Further to these key points is cost-effectiveness. In a recent study the cost-effectiveness of intracameral cefuroxime administration was analysed.\(^9\) Sharifi et al. examined various antibiotic options for the prevention of endophthalmitis.\(^9\) Using a cost-effectiveness model they found that intracameral cefuroxime is relatively cost-effective.\(^9\) Additionally a study by Colin et al.,\(^20\) described the cost implications of endophthalmitis management. This study was performed in France and found that the average hospital cost was €3688 per patient, totalling €636119 per annum for all public and private hospitalizations, including €223723 as day care.\(^20\)

### Current limitations

As with most treatment modalities there are limitations. One that was highlighted by both Prof. Alió and Prof. Behndig was the proportion of bacterial strains resistant to cefuroxime.

Although the proportion of these strains was relatively small before the introduction of cefuroxime, it is now larger because the overall rate of postoperative endophthalmitis incidence is decreasing. \"However,\" asserted Prof. Behndig, \"it is important to remember that the absolute number of endophthalmitis cases caused by strains resistant to cefuroxime have not increased in Sweden over the years, the resistant bacteria we have seen have been resistant all along so we have not induced any resistance to bacteria by using this antibiotic prophylaxis.\"

Additionally, it is very difficult to collect evidence proving the medical efficacy, which is something that all speakers agreed upon. \"You must keep in mind that endophthalmitis is not a game that you can play with evidence-based data, you need to prove you have performed your job properly,\" added Prof. Alió. \"Operation room pre-op asepsis measures are important... Other surgical factors have to be considered, in riskier cases in particular we have to decide on the location and architecture of the incision carefully to ensure better wound stability, which is a good preventative measure.\"

Prof. Cochener emphasized a prominent limitation with cefuroxime. \"Major limitations with cefuroxime are the difficulties encountered when preparing the product,\" she said. This has rung true for many ophthalmology practices and regulatory bodies as the lack of a commercially available preparation has meant increased concerns regarding the potential risk of error in dilution.\(^12–15\)

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**Table 2: List of prospective and retrospective studies examining the efficacy of intracameral cefuroxime as antibiotic prophylaxis for post-cataract surgery endophthalmitis prevention.**

<table>
<thead>
<tr>
<th>Country Team</th>
<th>Study period</th>
<th>Number of patients</th>
<th>Number of cases</th>
<th>POE incidence rate*</th>
<th>Previous POE incidence rate reported*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden Montan, 2002a, b</td>
<td>Jan 1996 to Dec 2000</td>
<td>32180</td>
<td>20</td>
<td>0.06%</td>
<td>0.26%</td>
</tr>
<tr>
<td>Sweden Wejde, 2005</td>
<td>Jan 1999 to Dec 2001</td>
<td>188151</td>
<td>112</td>
<td>0.0595%</td>
<td>0.26%</td>
</tr>
<tr>
<td>Sweden Lundström, 2007</td>
<td>Jan 2002 to Dec 2004</td>
<td>225471</td>
<td>109</td>
<td>0.048%</td>
<td>0.26%</td>
</tr>
<tr>
<td>Spain Diez, 2009</td>
<td>Oct 2003 to Sep 2008</td>
<td>4281</td>
<td>5</td>
<td>0.11%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Spain Garcia-Saenz, 2010</td>
<td>Jan 1999 to Sept 2005</td>
<td>6595</td>
<td>39</td>
<td>-</td>
<td>0.590%</td>
</tr>
<tr>
<td></td>
<td>Oct 2005 to Dec 2008</td>
<td>7057</td>
<td>3</td>
<td>0.043%</td>
<td>-</td>
</tr>
<tr>
<td>France Gualino, 2010</td>
<td>Jan 2007 to Dec 2008</td>
<td>3316</td>
<td>2</td>
<td>0.06%</td>
<td>0.2 to 0.3%</td>
</tr>
<tr>
<td>UK Yu WaiMan, 2008</td>
<td>Jan 2000 to Nov 2003</td>
<td>19425</td>
<td>27</td>
<td>-</td>
<td>0.139%</td>
</tr>
<tr>
<td></td>
<td>Nov 2003 to Dec 2006</td>
<td>17318</td>
<td>8</td>
<td>0.046%</td>
<td>-</td>
</tr>
</tbody>
</table>

* Previous postoperative incidence (POE) rate reported prior to the use of intracameral cefuroxime as a routine basis of prophylaxis regimen

Prospective and retrospective studies all over Europe substantiated the efficacy of intracameral cefuroxime in POE.
Currently, the preparation of cefuroxime for intracameral injection has been performed manually, and must be done on the same day as surgery as a result of the low stability of cefuroxime in solution. In this preparation, the cefuroxime is directly diluted into a saline solution, however, a large problem with this method is that dilution is required twice, increasing the risk of dilution error.

In light of this, Laboratoires Théa has introduced Aprokam®, which is the first intracameral cefuroxime approved as a pharmaceutical product and indicated in antibiotic prophylaxis of postoperative endophthalmitis after cataract surgery. “This new product provides the antibiotic prophylaxis, cefuroxime, in one single reconstitution (to obtain the recommended dosage), saving time, decreasing the risk of errors and complying with legal issues,” said Prof. Cochener.

Focusing on the preparation of cefuroxime for intracameral injection, Prof. Cochener remarked that a simplified procedure is required. This unmet need is supported in the literature as a limitation of cefuroxime use. “Going to the magistral preparation, there is first dilution of 750 mg of cefuroxime in 7.5 mL of solvent and you can see here there is already a potential risk of error of dilution,” she added. “Then at the second step, you prepare the solution for a second dilution, which further increases the risk of error. You dilute 0.1 mL of the initial preparation with 0.9 mL of the solvent. Finally, you keep 0.1 mL of the final double diluted solution for intracameral injection.”

Endophthalmitis is a devastating condition that must be prevented as treatment of this problem, although achievable, results in poor visual acuity or potentially even blindness. Through numerous studies, it has been proven that the use of antibiotic prophylaxis can effectively achieve prevention of the majority of strains of bacterial endophthalmitis. Intracameral cefuroxime use has also been proven to be cost effective in the prevention of this condition by decreasing the total cost (direct and indirect) of endophthalmitis. Intracameral cefuroxime use has also been proven as treatment of this problem, although achievable, results in poor visual acuity or potentially even blindness. Through numerous studies, it has been proven that the use of antibiotic prophylaxis can effectively achieve prevention of the majority of strains of bacterial endophthalmitis. Intracameral cefuroxime use has also been proven to be cost effective in the prevention of this condition by decreasing the total cost (direct and indirect) of endophthalmitis.

As Prof. Behndig had stressed earlier based on his experiences in Sweden, the high frequency of cataract operations and high demands of patients for perfect results has led to the need for an effective and secure solution to the threat of postoperative endophthalmitis following this procedure.

However, there has been a lack of a commercially available preparation of cefuroxime for intracameral use until now, which has hindered the uptake of this method as general standard practice.

After having proven the efficacy of intracameral cefuroxime injected at the end of cataract surgery in reducing the risk of contracting endophthalmitis by fivefold, the second objective of the ESCRs study, as highlighted by Prof. Barry, was to encourage industry to come up with an approved commercial product. Thanks to the simplified preparation now available from Laboratoires Théa, Aprokam®, which has been European approved for use as intracameral cefuroxime approved as a pharmaceutical product and indicated in antibiotic prophylaxis of postoperative endophthalmitis after cataract surgery, there is now a commercially available preparation. “We now have a European Medicines Agency product available and I’m glad to hear that,” Prof. Barry said.

So, with the Aprokam® single reconstitution, a lot of these potential risk factors can be eliminated. “Now, onto the Aprokam® preparation,” she continued, “only one reconstitution is required into 5 mL of solvent and it’s recommended only to use saline solution and the reconstitution is performed directly into the vial improving security by limiting the exposure of the sterile solution to the ambient air and time spent preparing the syringe.”

“As you can see with the magistral preparation it’s obviously the double dilution that is the most risky parameter,” said Prof. Cochener. “Aprokam® is the only product that has the official indication as intracameral cefuroxime approved as a pharmaceutical product and indicated in antibiotic prophylaxis of postoperative endophthalmitis after cataract surgery. Additional advantages include traceability of course. When it comes from the pharmacy it is well guaranteed but with Aprokam® there is a label provided. There is also the interest of requiring one vial per patient.”

In looking at pricing, which is something that Prof. Cochener noted was a current focus, she said that outside assistance from a pharmacy would not be required anymore with the simple preparation afforded by this new approved commercial product.

“So, I would say that it is a simple and clear protocol, one unique solvent, preparation directly in the operating room and the conclusion can also underline that it is very easy to reconstitute and the security was exactly what we were looking for,” said Prof. Cochener.

Endophthalmitis is a devastating condition that must be prevented as treatment of this problem, although achievable, results in poor visual acuity or potentially even blindness. Through numerous studies, it has been proven that the use of antibiotic prophylaxis can effectively achieve prevention of the majority of strains of bacterial endophthalmitis. Intracameral cefuroxime use has also been proven to be cost effective in the prevention of this condition by decreasing the total cost (direct and indirect) of endophthalmitis. As Prof. Behndig had stressed earlier based on his experiences in Sweden, the high frequency of cataract operations and high demands of patients for perfect results has led to the need for an effective and secure solution to the threat of postoperative endophthalmitis following this procedure.

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