SIMPLIFIED MANAGEMENT OF THE CATARACT PATIENT

Laboratoires Théa Satellite Symposium
XXXV Congress of the ESCRS

8 October 2017
Lisbon, Portugal
The goal of this meeting is to spread the message that this new product, Mydrane™, really has the potential to improve the management of cataract surgery. It makes for more efficient and safer surgery because we know that keeping the pupil dilated and stable during cataract and other lens replacement procedures is critical. Intraoperative miosis increases the difficulty of these procedures and makes complications more likely," said Prof Tassignon. "While appropriate mydriasis is usually achieved by the administration of topical eye drops, their use has clear drawbacks in terms of the time needed to dilate the pupil and the risk of systemic side-effects, she said. "That is why ophthalmologists have been looking for alternatives to improve on current methods. Today’s symposium will give us the opportunity to hear about the possible benefits of a new intracameral approach to maintain stable intraoperative mydriasis and reduce side-effects," she said.

MYDRANE 0.2 mg/ml + 3.1 mg/ml + 10 mg/ml solution for injection. Composition: 1 ml of solution for injection contains 0.2 mg of tropicamide, 3.1 mg of phenylephrine hydrochloride and 10 mg of lidocaine hydrochloride. Excipients. Indications: MYDRANE is indicated for cataract surgery to obtain mydriasis and intraocular anaesthesia during the surgical procedure. MYDRANE is indicated in adults only. Posology: MYDRANE should only be used in patients who have already demonstrated, at pre-operative assessment, a satisfactory pupil dilation with topical mydriatic therapy. Slowly inject, by intracameral route, 0.2 ml of MYDRANE in only one injection, at the start of the surgical procedure. Contraindications: Hypersensitivity to the active substances (tropicamide, phenylephrine hydrochloride and lidocaine hydrochloride) or to any of the excipients. Known hypersensitivity to anaesthetics of the amide type. Known hypersensitivity to atropine derivatives. Pregnancy: MYDRANE should not be used during pregnancy. Breastfeeding: MYDRANE should not be used during breast feeding. Undesirable effects: Nervous system disorders (uncommon): Headache. Eye disorders (uncommon): Keratitis, Cystoid macular oedema. Intraocular pressure increased. Posterior capsule rupture, Ocular hyperaemia. Vascular disorders (uncommon): Hypertension. Nature and contents of container: One 1 ml sterile brown glass (type I) ampoule filled with 0.6 ml of solution for injection, per paper/PVC blister. Box of 1, 20 and 100 ampoules together with respectively 1, 20 and 100, 5-micron sterile filter needles. Not all pack sizes may be marketed. Marketing Authorisation Holder: Laboratoires THEA – 12, Rue Louis Bleriot – 63017 Clermont-Ferrand Cedex 2 – France – Tel: +33 4 73 98 14 36. Marketing Authorisation Number(s): To be completed nationally. DATE OF EUROPEAN AUTHORISATION: 02 JUL 2015. Detailed information on this medicinal product is available on the website of local Health Agency. DATE OF REVISION OF THE TEXT: 29 SEPT 2017.
The potential benefits of big data in assessing the safety and efficacy of intracameral cefuroxime

Professor Vincent Dainen MD, PhD, University Hospital Montpellier, France

Large population-based health administrative databases, clinical registries and data linkage systems are a rapidly expanding resource for health research. These sources of “big data” can be used in ophthalmology to augment our knowledge of disease surveillance and outcomes and the use of health resources, and provide a valuable supplement to the data contained in randomised clinical trials and other peer-reviewed scientific literature.

A large part of my own recent research has focused on using big data to assess the efficacy and safety of intracameral cefuroxime at the end of cataract surgery for the prevention of endophthalmitis. The idea is essentially to add “real-world evidence” to the pool of knowledge concerning a particular disease, device or therapy, thereby allowing clinicians to make better informed decisions for the benefit of their patients.

The European Medicines Agency (EMA) defines “real-world evidence” as all the data collected outside randomised clinical trials. Randomised clinical trials (RCTs) do not have sufficient power to assess rare adverse events such as endophthalmitis. In the United States, the Food and Drug Administration (FDA) recognises many sources of big data and it now recommends including real-world evidence data for future and new drug applications.

Despite the landmark ESCRS study some years ago led by Peter Barry, the use of intracameral cefuroxime has still not been fully adopted in cataract practices globally. In 2012, the EMA approved in six European countries the first premixed intracameral cefuroxime formulation for endophthalmitis prophylaxis (Aprokam™, Laboratoires Théa). Big data can also help in applying real-world evidence to the utility of using cefuroxime in cases of posterior capsular rupture, which is the major risk factor of endophthalmitis (Figure 1).

Nevertheless, significant differences exist in the recommendations in the use of cefuroxime between countries, even European ones. Some concern was also raised in some quarters concerning potential retinal toxicity from the use of intracameral cefuroxime, although inaccurate preparation of the cefuroxime preparation seems to have been responsible for this. There is also an enduring controversy in the United States, where many surgeons use vancomycin at the end of cataract surgery to prevent endophthalmitis and where its use has been implicated in several cases of haemorrhagic occlusive retinal vasculitis (HORV).

In France, we are fortunate to have excellent administrative medical care records, which provide an abundance of information: demographic data, medical data, out-of-hospital reimbursements, hospitalisation, diagnosis and data updates. In 2016, Professor Catherine Creuzot-Garcher published a study looking at the incidence of acute postoperative endophthalmitis after cataract surgery, which clearly showed that the endophthalmitis rates decreased with increasing use of cefuroxime between 2005 and 2014. In 2005, the incidence of endophthalmitis was 0.145%, which went down to 0.053% in 2014. In multivariate analysis, intraoperative posterior capsule rupture, combined surgery and male gender were associated with a higher risk of acute postoperative endophthalmitis.

In another study published last year we sought to assess the effectiveness and retinal safety of an intracameral injection of cefuroxime sodium for the prevention of endophthalmitis and its possible use in cases of a perioperative capsular rupture of the lens.

We looked at more than 2 million cataract patients between 2010 and 2014 and concluded that the risk of postoperative endophthalmitis was reduced with the use of cefuroxime and that retinal safety was not increased for patients receiving cefuroxime injections. For patients with a perioperative capsular rupture of the lens, the incidence of endophthalmitis was lower for those who received an injection of cefuroxime than for those who did not (0.37% vs 0.51%, respectively), whereas an increased risk of cystoid macular oedema was not identified for those who received or did not receive an injection of cefuroxime (5.6% vs 7.3%, respectively).

Our conclusion was that in routine practice the intracameral injection of cefuroxime at the end of cataract surgery is associated with a lower risk of postoperative endophthalmitis and is safe for patients with or without a perioperative capsular rupture.

While these data might be used to support the consideration of the routine use of cefuroxime to prevent postoperative endophthalmitis, in the absence of a randomised clinical trial they cannot prove a direct cause-and-effect relationship between the injection of cefuroxime and postoperative endophthalmitis.


Polish surgeons’ experience and satisfaction levels using Mydrane™, the first intracameral combination of mydriatic and anaesthetic

Dariusz Kęcik MD, PhD, Department of Ophthalmology Medical University of Warsaw, Poland

The tools, techniques and technology used in cataract surgery have changed radically over the course of time and our methods for removing the opaque lens have become ever-more sophisticated. Nevertheless, despite this evolution, two key elements of the cataract procedure have remained essentially the same: mydriasis and anaesthesia.

In 2015, a new product, Mydrane™, was introduced to the market. It is the first ready-to-use, standardised, commercially manufactured medicinal product indicated for cataract surgery to obtain mydriasis and intraocular anaesthesia approved in several European countries, including Poland. It is administered to the anterior chamber at the beginning of cataract surgery.

While those of us who tested the product knew that Mydrane™ worked very well, there still remained the question of what actually determines our choice of mydriatic agent to use in cataract surgery. There are many aspects to this issue – clinical trial results, scientific literature, risk of complications, possible alternatives, efficacy, legal regulations, surgeons' opinions, ease of use and price are all factors that can play a role in our decision-making. However, ultimately it is the doctors who decide based on their everyday clinical experience and practice requirements.

To try to gather some hard data on this, we initiated an observational register trial of patients undergoing cataract surgery at several centres in Poland for whom Mydrane was used for mydriasis and intraocular anaesthesia. The primary objective was to evaluate the effect of Mydrane™ on the pupil size at each key point of the cataract surgery. The secondary objective was to evaluate the effect of using Mydrane™ on the time needed to obtain mydriasis as well as its stability for the duration of the procedure in the opinion of surgeons performing the surgery. The trial started in February 2017 in seven university hospitals, and included 307 patients in whom the pupil could be dilated to 6.0mm or more during preoperative check-up.

As one might expect from a population group undergoing cataract surgery, the patient population in our study had many comorbidities: hypertension in 241, diabetes in 72, prostate disease in 29 and depression in 17. Ocular diseases in addition to cataract included glaucoma in 41 patients, dry AMD in 13, wet AMD in six, diabetic retinopathy in four and other eye diseases in 36 patients.

Immediately after surgery, the operating surgeons’ opinions on the time to obtain mydriasis and the stability of mydriasis were collected on a five-point Likert Scale. The Likert Scale is used to allow respondents to express how much they agree or disagree with a particular statement. Two questions were asked: firstly, whether mydriasis was obtained in a short time after administration of Mydrane™, and secondly, whether the mydriasis was stable after the drug was injected into the anterior chamber.

The mean pupil diameter was 2.3mm just before the start of the surgery and was measured at key steps thereafter: the mean dilation was 7.0mm just before capsulorhexis, 6.9mm just before implantation of the intraocular lens and 6.6mm just before the end of the surgery (Figure 1).

In terms of whether mydriasis was obtained quickly after administration, 92% of respondents agreed or strongly agreed (Figure 2). Only in 1% of cases, or three procedures, did surgeons strongly disagree. For the stability of the mydriasis, 88% agreed or strongly agreed that it remained stable throughout the procedure and just 1% strongly disagreed (Figure 3).

In conclusion, the study clearly showed that mydriasis obtained using Mydrane™ during cataract surgery was fast and stable in nearly 90% of real-life cases in the opinion of surgeons. The study results confirmed my own clinical experience that stable mydriasis may be achieved after a single, intracameral administration of Mydrane™ at the beginning of cataract surgery without preoperative dilation in a real-life patient population.
Cataract surgery is the most frequent procedure performed in ophthalmic surgery, and obtaining optimal stable mydriasis and anaesthesia remains fundamental to ensuring consistent outcomes for today’s patients. Topical eye drops have been the mainstay of mydriasis in the modern cataract era, but the drawbacks of this approach are well known: it requires considerable staff resources, is time-consuming and carries the risk of systemic overdosing and toxicity for the corneal epithelium. Its efficacy is also limited, with secondary administration of mydriatics frequently required intraoperatively to avoid complications associated with constricted pupils.

To address the shortcomings of eye drops and custom-blended formulations, Laboratoires Théa combined a solution of two mydriatics, phenylephrine 0.31% and tropicamide 0.02%, and an anaesthetic (lidocaine 1%) in one product, Mydrane™, designed for single-use intracameral injection in cataract surgery.

At the beginning of the surgery, 200μL of Mydrane™ is slowly injected in one intracameral injection by the surgeon through the side port or principal port. The onset of action is extremely rapid, with 95% of maximal dilation achieved in 30 seconds after administration of Mydrane™.

As well as standard cataract cases, I have also successfully used Mydrane™ in more complicated cases where the maintenance of stable mydriasis really makes a difference to the final outcome.

One recent patient of mine, a 68-year-old female with glaucoma, is a good example of the benefits that Mydrane™ brings to more challenging cataract surgery cases. Her right eye was scheduled for cataract removal, she was non-diabetic and her glaucoma was being treated with prostaglandin beta-blocker drops once a day.

Preoperatively, we tested the quality of the dilation of her pupil with tropicamide (two drops in five minutes) and neosynephrine (two drops in five minutes). The pupil dilation was greater than 7.0mm in the 10 minutes after the second instillation, so we deemed this patient eligible for Mydrane™. Immediately before surgery, we inserted two drops of oxybuprocaine in two minutes, followed by three separate washes with povidone iodine.
Pupil dilation is an important component of successful cataract surgery – as surgeons, we want to have optimal visualisation of the intraocular structures including the iris and the capsule, and we like to obtain sufficient dilation in order to have a well-centred and adequately sized anterior capsulorhexis.

While “adequate dilation” is a subjective term, most surgeons would probably agree that it means more than 6.0mm and ideally 7.0mm or 8.0mm. Pupil constriction can occur intraoperatively for a variety of reasons. Surgical trauma, prostaglandin release and intraoperative floppy iris syndrome, for example, can all generate perioperative miosis.

Surgically induced miosis during cataract surgery is also associated with a higher risk of complications, such as posterior capsule rupture, iris trauma, uveitis and vitreous loss. In cases where the pupil is relatively small, the capsulorhexis obtained with external or additional callipers will also be smaller, making nuclear disassembly more difficult, increasing the risk of iris injury and reducing visualisation, both during cortex removal and intraocular lens implantation.

Pupil dilation is also important for the optimal positioning of intraocular lenses, and especially in multifocal and toric lenses where correct alignment is mandatory in order to achieve the best possible visual outcome for the patient. Proper dilation also minimises the risk of leaving retained soft lens matter behind the iris.

During surgery, it is normal to experience some miosis. This occurs due to the surgical trauma, and will happen irrespective of the skill of the surgeon, as cataract removal remains a trauma for the eye with subsequent release of prostaglandins. There are also other patient-related factors that may influence the incidence of miosis during the surgery.

Prior to Mydrane™, I used an intracameral mydriatic containing a mixture of adrenaline and Xylocaine. However, the patients were definitely less comfortable with this approach and could feel the injection, whereas with Mydrane™ the combination of lidocaine, tropicamide and phenylephrine makes for a completely painless experience for the patient.

I usually use a ring calliper with an internal diameter of 5.0mm in my surgeries in order to optimise the size, shape and centration of the capsulorhexis. The effective pupil dilation achieved with Mydrane™ enables the calliper to guide the surgeon in creating the optimal capsulorhexis shape and centration (Figure 1).

Overall, intracameral mydriatics with Mydrane™ offers cataract surgeons a rapid, effective and safe alternative to topical mydriatics in phacoemulsification surgery, and improves the experience for our patients as well.

From a patient and surgeon perspective, the ideal mydriatic should be easy to administer, offer pain-free surgery, be well tolerated in the eye and have low systemic side-effects. Mydrane™ ticks all of these boxes. It also allows us to work more swiftly in the OR and removes the risk of mistakes in mixture preparation, as was the case with previous intracameral mydriatics.

Another major advantage from my perspective is the fact that the mydriasis effect endures and even augments over the course of the surgery. This is a welcome contrast to topical drop dilation, where the effect wears off as the surgery progresses. Overall, intracameral mydriatics with Mydrane™ offers cataract surgeons a rapid, effective and safe alternative to topical mydriatics in phacoemulsification surgery, and improves the experience for our patients as well.
Sweden was one of the earliest adopters of intracameral mydriatics (ICM) in cataract surgery, and has successfully used this approach in hundreds-of-thousands of cataract procedures carried out since 2003. ICM is currently used in more than 50% of Swedish cataract and refractive lens exchange (RLE) procedures. Although we are currently in the process of switching to Mydrane™ in our clinic, we previously used a similar solution that was prepared by the Swedish national pharmacy.

The impetus for my personal long-standing interest in mydriatics initially stemmed from the realisation in 2002 that we were spending about 80% of surgery time in our clinic dilating the pupil and 20% performing the surgery. Such a situation was clearly far from satisfactory, leading to an inefficient use of clinical resources and time. I always felt that the ratio should be the other way around: 20%, or less, of dilation time and 80% operation time.

The disadvantages of topical mydriatics are well known: they offer a slow onset, carry the risk of systemic side-effects and offer no guarantee against intraoperative pupil constriction. This latter problem was solved to some degree in Sweden, however, with the addition of epinephrine irrigation to the infusion bottle. The formulations that we used initially were lidocaine 1%, cyclopentolate 0.1% and phenylephrine 1.5%, and subsequently lidocaine 1% and phenylephrine 1.5%. The current formulation, as contained in Mydrane™, is lidocaine 1%, tropicamide 0.02% and phenylephrine 0.31%.

This formulation has a neutral pH value and I think that is the reason why it is not felt by the patients when it is injected into the anterior chamber. This is an advantage compared to the mixture we used in Sweden, so it is another step forward. The mydriatic effect is very rapid and the patient feels less light sensitivity (Figure 1) at the beginning of the procedure than with topical mydriatics. We proved this in an earlier study, which also showed that the visual rehabilitation with ICM and drops is equally fast (Figure 2).

A systemic exposure study that we carried out looking at 271 patients administered with Mydrane™ and 281 patients with topical mydriatics found that tropicamide plasma levels were below quantification with Mydrane™ but detectable in all cases with topical mydriatics. Phenylephrine was also detectable in 14.3% of Mydrane™ patients and in all reference treatment patients for at least one time point.

A phase III study has also been carried out looking at 555 patients randomised between Mydrane™ and topical mydriatics. It was a non-inferiority design with both groups achieving adequate mydriasis (more than 7.0mm) during capsulorhexis, phacoemulsification and IOL insertion. There was a higher proportion of uncomplicated IOL insertions and better patient comfort with Mydrane™, possibly because the mydriasis is more stable with that substance.

We also carried out some evaluations of Swedish surgeons’ preferences, and found similar findings to those reported by Dr Kęcik for Polish surgeons in terms of the ease of use of ICM as an effective and safe alternative to standard eye drops for initiating and maintaining intraoperative mydriasis and analgesia.

The superior patient comfort with Mydrane™ was also confirmed by a comparative study we conducted in 2014 on ICM in bilateral RLE on 56 patients. These were same-day bilateral RLE cases who randomly received topical mydriatics in one eye and ICM in the fellow eye. We assessed pupil sizes and perceived pain/discomfort and glare during the procedure. What was striking was that when we looked at the videos of the surgeries afterward, we noticed a discernible iris billowing in 17 eyes with topical mydriatics but in only one eye with Mydrane™. These 50-year-old RLE patients are not the easiest to operate on, so using ICM really stabilises the pupil and makes the surgery easier. We experienced no cases of floppy iris or iris prolapse in this series, but the iris billowing was easily discernible in those eyes treated with topical mydriatics.

Since introducing ICM in Sweden in the early 2000s, we have seen that 97% of the overall operating time is now spent on surgery and just 3% on pupil dilation. I think that represents a far more satisfactory statistic, and suggests that intracameral mydriatics with Mydrane™ will continue to have a major role to play in ensuring safe and efficient modern cataract surgery for our patients.

Figure 1. ICM gives less light sensitivity at the initiation of surgery

Figure 2. Rapid visual rehabilitation
The advantages of drop-less management in cataract surgery

Prof José Güell, Associate Professor of Ophthalmology at the Autonomous University of Barcelona

The Mydrane™ combination of anaesthetic lidocaine 1%, phenylephrine 0.31% and tropicamide 0.02% in one solution has the potential to radically transform the way we perform cataract surgery. It matches the concept of lean healthcare methodology, which is designed to improve patient pathways, reduce the time spent at the hospital, reduce waste and improve the overall patient experience.

It also induces several beneficial changes for the entire team in the cataract service. For the nurse, it greatly simplifies the preparation of the patient. For the surgeon, it means far less waiting time before the surgery can commence. For the patient, it makes for a more comfortable experience, with reduced stress waiting on the mydriatics to take effect and a pain-free procedure once Mydrane™ has been administered.

To coincide with the launch of Mydrane™ in Spain, Laboratoires Théa applied the lean healthcare methodology between September 2016 and June 2017 to highlight the potential benefit of intracameral mydriasis for the organisation of cataract services in clinics and hospitals.

Based on the Toyota car manufacturing model, the lean concept focuses on how efficiently resources are being used and asks what value is being added for the customer in every step of the process. The healthcare industry has demonstrated some success in recent years in applying these principles in the United States, United Kingdom, Australia and Canada.

The approach has also yielded promising results in Spain. Starting in October 2014, implementing the lean approach at the emergency department of a Barcelona hospital resulted in significant improvements: before lean, a patient going through level 3 of the emergency department took up to 300 minutes, whereas after lean, it took 180 minutes for 90% of patients.

Applying the lean model to cataract surgery (from arrival through to postoperative discharge) should therefore make it possible to minimise waiting times, reduce waste and improve the management of unexpected events.

Using Mydrane™ as part of this new protocol should also deliver major efficiency gains: operations should begin on time, as there is no delay waiting for mydriasis to take effect. We can expect a 45% reduction in global patient time at the hospital and a 70% reduction in patient preparation time. Furthermore, sources of error and variability in administration of the medication are reduced, and there is a reduction of nursing workload, with a direct impact on the quality of the process and care of the patient.

We already know from studies that there is enhanced patient comfort during capsulorhexis and IOL implantation using Mydrane™. It enables good and stable mydriasis until the end of surgery with less pain or sensation of pressure in the eye for the patient.

A recent prospective study on 120 patients in the United Kingdom evaluated intracameral versus topical mydriasis in cataract surgery in a standard hospital in terms of patient satisfaction, patient flow and resources.1

The study showed that patients with Mydrane™ spent less time in the department compared to those administered with topical drops (87 minutes versus 146 minutes). The time spent administering eye drops was 70% more than with intracameral Mydrane™. The nursing workload was reduced with ICM, leaving nurses free to perform other tasks. Mydrane™ was also associated with an improved patient experience, with 66% satisfied with eye drops and 76% with Mydrane™.

Using intracameral mydriatics as part of a lean healthcare model should also result in cost savings that accrue due to reduced waiting times and improved use of resources. Overall, Mydrane™ allows for better management of the cataract surgery service – delivering enhanced performance, efficacy, stability, quality and patient experience. The future of cataract surgery undoubtedly lies in intracameral mydriasis with minimal toxicity, less nursing time and greatly improved efficiency in the operating room.