NOK 2012 HELSINKI

September 2012

Preserving Vision in Chronic Diseases

Scientific Symposium held at the 40th NOK Meeting in Helsinki

More than 400 ophthalmologists mainly from the Nordic, the Baltic and Eastern Europe countries followed an invitation from Santen to attend a symposium held during the 40th Nordic Ophthalmic Congress (NOK) taking place in Helsinki, Finland. The focus of the symposium was related to preventive medicine of chronic ophthalmic diseases such as glaucoma and ocular surface disease: Prof. Johan Stjernschantz (University of Uppsala, Sweden) presented the pharmacology of Tafluprost and discussed the question if prostaglandins can be further improved. Prof. Anders Bergstöm (Skane University, Sweden) provided an overview on the success factors for surgical procedures in glaucoma. In another presentation Prof. Ingrida Janulevičienė (Lithuanian University of Kaunas, Lithuania) presented new data of the impact of a preservative-free glaucoma medication on tear-film osmolarity and Quality of life of glaucoma patients. And finally, data from clinical studies with an innovative cationic oil-in-water emulsion (Cationorm®) for the treatment of symptoms of ocular surface disease (OSD) were presented by Jean-Sebastien Garrique, Director of Research & Development at Novagali, France. The symposium was chaired by Prof. Hannu Uusitalo (Finland).

Prof. Hannu Uusitalo chaired the symposium

Pharmacology of prostaglandin analogues

According to J. Stjernschantz (Sweden), the ring-structure at the omega-chain – common for all prostaglandin-analogues (PGA's) - is responsible for their selectivity at the prostanoid FP receptor. In contrast the natural occurring prostaglandin PGF2α is non-selective compared to the synthetic compounds that were used in glaucoma treatment. Tafluprost the latest development that was introduced for the medical management of glaucoma and ocular hypertension shows the highest selectivity for the FP-receptor and a lower affinity to the EP2-receptor compared with other PGA's.[1,2] The compound is very effective. All compounds from the PGA family of drugs work mainly by an increase of uveoscleral outflow.[3] J. Stjernschantz pointed out that about 70% of the effect of PGA's is due to the improved uveoscleral pathway and another 30% due to an effect on trabecular meshwork leading to an improved trabecular outflow facility.

Tafluprost with comparable IOP lowering effect as Latanoprost

All PGA's have about the same efficacy. Studies comparing the efficacy of Tafluprost and Latanoprost show an equal or a comparable efficacy of both compounds (Figure 1).[4,5] Major difference to other PGA's is that Tafluprost is currently the only PGA that is available in a preservative-free formulation which is clearly beneficial for many patients.

TOPICS

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Prof. Stjernschantz discussed possible improvements of PGA's

Can PGA's be futher improved?

J. Stjernschantz gave his evaluation on the question if PGA's can be further improved. In this context, an improvement can be related to the reduction of side-effects, such as conjunctival hyperaemia, iris-hyperpigmentation, eyelid pigmentation and eyelash-growth. Also one could speculate if there are options to increase the efficacy of these compounds. One of the major issues with PGA's is the occurrence of a conjunctival hyperaemia: All PGA's except thromboxane (and other TP re-ceptor agonists) cause hyperaemia.However, TP receptor agonists should be avoided because these compounds induce a marked vasoconstriction, platelet aggregation and therefore may cause harmful side effects such as thrombosis. The hyperaemic side effect is difficult to avoid completely because this effect is rather complex and cannot only be linked to a vasodilatation.

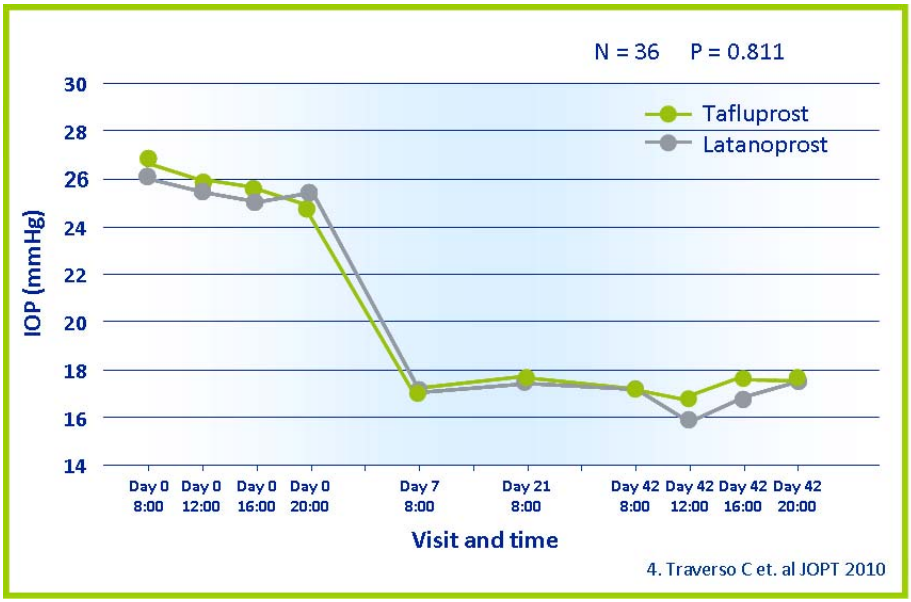


Figure 1: IOP lowering effect of Tafluprost compared to Latanoprost

Nociception, irritation and pain are probably not mediated through FP or EP2 prostanoid receptors. Thus using compounds that are highly selective for these prostanoid receptors avoid these side effects. Unfortunately iridial and epidermal melanogenesis seems clearly be linked to the FP prostanoid receptor: It could be shown by studying the transcription of prostanoid receptor genes in isolated human iridial melanocytes using PCR that this effect is clearly linked to the stimulation of the prostanoid FP receptor.[6] Individuals with totally blue eyes have a mutation in their HERC gene controlling the promotor of the OCA-2 gene. This could explain why pigment is not formed in iridial melanocytes of blue-eyed persons when treated with FP receptor agonists.[7,8]

SUMMARY AND CONCLUSIONS

- **Tafluprost is a highly potent, selective FP prosta-noid receptor agonist with a slight spill-over effect on the EP3 prostanoid receptor**
- **Tafluprost has been shown to reduce IOP primarily by enhancing uveoscleral outflow of aqueous humour**
- **Tafluprost has similar IOP reducing effect as the other prostaglandin analogues**
- **To improve the pharmacological characteristics of PGA's in glaucoma eyedrops appears to be difficult**
- **A better approach to improve the medication may be to optimize the formulation e.g. by developing preservative-free formulations**
- **Tafluprost is the only PGA that is currently available as preservative-free ophthalmic solution**
- **Preservative-free Tafluprost has a low hyperaemia rate**
- **To enhance the IOP-reducing effect combination of the PGA with other IOP-reducing medications, e.g. beta-blockers would appear to be the easiest, preferably in preservative-free formulations**

Also the hypotrichotic effect of the eyelashes seems to be linked to the stimulation of the FP receptors in melanocytes of hair follicles.[9]

Possible options to improve PGA's for glaucoma treatment

In principal there are three different possible approaches to improve PGA's for the treatment of glaucoma: Firstly one could improve the pharmacological characteristics of the PGA, secondly the formulation of the product could be improved and thirdly and finally the IOP lowering effect of a PGA could be improved by combining the compound with other IOP lowering compounds. To modify the PGA molecule seems rather difficult because most of the side effects are linked to the receptors that were important for achieving the excellent IOP lowering efficacy. Obviously there are differences in the hyperaemia rates between the different PGA's and a good approach is to improve the formulation of the PGA and for example to remove the preservative BAK.[10-14] This has been done during the development of preservative-free Tafluprost by Santen with the result of a lower rate of hyperaemia as shown in Figure 2. An increase of the IOP lowering effect also seems difficult to be achieved by modifying PGA compounds. However a combination of PGA's with other IOP lowering medications (Betablockers, Alpha-2-Agonists, Carbonic anhydrase inhibitors) may help to achieve lower target pressures.

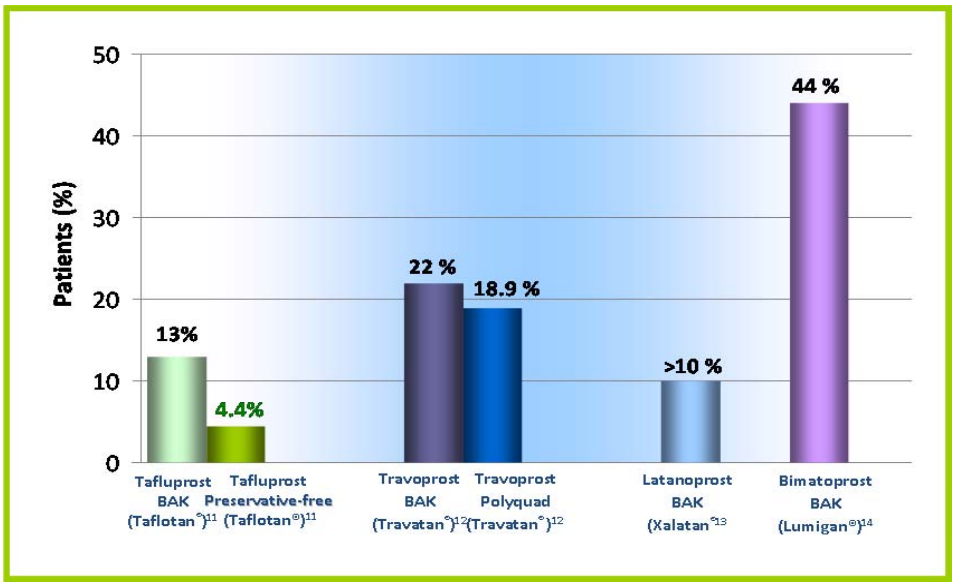


Figure 2: Hyperaemia rates of different PGA formulations.

Success Factors in Glaucoma Surgery

There are several key success factors for glaucoma surgery which were discussed by Anders Bergström (Sweden): Most important for success are to choose the right cases, to care about the pre-operative medication, to choose a familiar procedure, to standardize and constantly improve the procedures used and to choose the right post operative medication (Figure 3).

- Choose the right cases
  - Virgin eyes
  - Moderate glaucomas
- Pre-surgical medication
  - Preservative free eye drops
- Choose a familiar procedure
  - Learn a few procedures that suits you
  - Trabeculectomy is a good standard choice
- Standardize
  - Do your procedure in the same way all the time
- Post operative care

Figure 3: Success-factors for glaucoma surgery

Prof. Bergström presented critical success factors for glaucoma surgery

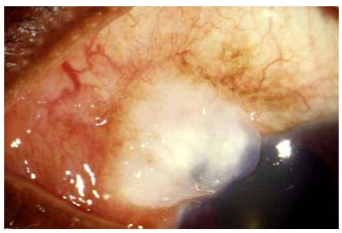
Choosing the right cases important

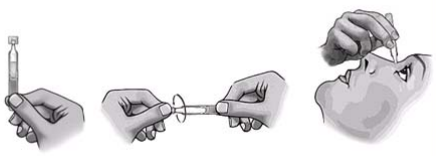
Previous surgical procedures, including filtration, retinal macular surgery and cataract surgery are increasing the risk of failure. Also other procedures such as strabismus surgery and conjunctival incisional surgical procedures are increasing the risk of failure. Secondary glaucomas such as neovascular and traumatic glaucomas have also a higher risk for failure. Furthermore, patients with advanced glaucomas, elderly and non-caucasian patients may bear a higher risk of failure.

Long-term medical glaucoma treatment with preserved eye drops is a risk factor

Long-term anti glaucoma therapy is associated with increased rates of surgical failure.[15-17] The risk of failure depends on the duration of treatment, the number of eye-drops used, the active substance (miotics, sympathomimetics) and the preservative (preserved or preservative-free). The use of BAK preserved eyedrops before surgery seems to be an important risk-factor: The toxicity of BAK is well established and it is known, that preserved solutions can result in an inflammatory response.[18-20] This chronic inflammation can lead to fibrosis and scarring, two factors that may lead to filtration failure. From this point of view, preservative-free solutions are the better choice according to A. Bergström (Figure 4). He also recommended considering a medical therapy with topical steroids starting one or two weeks before the surgical procedure.The right procedure increases the success rate of a surgical procedure. All surgical procedures have a learning curve and, according to A. Bergström, there are too many variants of glaucoma procedures to learn them all. He gave the advice to learn only a few of these possible procedures that suit to the attitude, knowledge and skills of the surgeon. Trabeculectomy is a good standard choice. The procedures that are used should be done in the same way all the time (limbus or fornix based conjunctival flap, same scleral flap shape and size, use of MMC, 5-FU or no antimetabolites, anterior segment infusion, type and numbers of sutures). However, not all cases are the same thus, from the standard once established one can modify and further improve.

- Toxicity of BAK is well established[18–20]
- Preserved solutions can result in inflammatory responses
- Chronic inflammation can lead to fibrosis and scarring
- Fibrosis and scarring can lead to filtration failure
- Preservative-free solutions are better





18. Chiambaretta et al. 1997. 19. Guenoun et al. 2005. 20. Buron et al. 2006

Figure 4: Preoperative eye drops are important for surgical success

SUMMARY AND CONCLUSIONS

- **In order to improve the outcome of glaucoma surgery it is important to choose the right cases**
- **Pre-operatively preserved eyedrops should be replaced with preservative-free solutions**
- **The surgeon should choose a familiar procedure and standardize this procedure**
- **Trabeculectomy is still the golden standard in glaucoma surgery**
- **Post-operative care is very important to increase the success rate of the surgical**

Prof. Janulevičienė emphasised the high prevalence of OSD in patients with glaucoma and presented new data on the effects of preservative-free Tafluprost on tear-film osmolarity.

Post-operative care is critical for success

Very important to consider is the post-operative care. Post-operative care may be even more important than surgery to achieve the best outcome. Factors to consider in this field are the use of steroids or/and NSAIDs, the use of mydriatics, antibiotics and post-op antimetabolites. Some patients may require a massage if the IOP increases or a needling.The Moorfields Safe Surgery System, which is available on the internet is a valuable tool to make the right choices.[21]

Effect of preservative-free therapy on tear-film, tolerability and IOP in glaucoma patients

Ingrida Janulevičienė (Lithuanian University of Health Sciences, Kaunas, Lithuania) started her presentation stating that compliance is very important in order to achieve the goal of glaucoma therapy. A good compliance is only achievable if the glaucoma medication is highly efficacious, safe and well tolerated. In order to achieve a high quality of life for the patient a good glaucoma medication requires the achievement of maximum efficacy with minimum number of IOP- lowering medications. Furthermore, coexisting conditions such as changes of the ocular surface and the tear-film should be considered.

High prevalence of OSD in patients with glaucoma

About one out of four outpatient visits is linked to patients with dry eye. The prevalence of OSD in patients with glaucoma is high: A paper published by Erb et al. shows that 53% of glaucoma patients suffer from dry eye.[22] Baudouin et al. confirm this with a prevalence of 51% of patients suffering on glaucoma and OSD, 21% of the patients having moderate to severe dry eye symptoms.[23] Leung et al. determined a prevalence of 59% of OSD in patients with ocular hypertension or glaucoma: Using different methodologies they concluded that 27% of the patients had severe symptoms (OSDI index), 35% had severe tear deficiency (Schirmer's test) and 65% had severe decrease in the quality of the tear-film (TBUT).[24] Further details are shown in figure 5.

Assessment	Observation
Ocular Surface Disease Index Questionnaire	• 59% of patients had symptoms in ≥1 eye • 27% had severe symptoms
Schirmer's Test	• 61% of patients had decreased tear production in ≥1 eye • 35% had severe tear deficiency
Corneal and conjunctival Lissamine Green Staining	• 22% of patients had positive staining • None had severe staining • Each additional benzalkonium chloride (BAK)-containing eye-drop associated with a 2x higher odds of abnormal lissamine green staining (odds ratio: 2.0; 95% CI: 1.1–3.9; *P*=0.034)
Tear Break-Up Time (TBUT)	• 78% of patients had abnormal tear quality • 65% had severe decrease in tear quality

Figure 5: Prevalence of OSD in patients with ocular hypertension or glaucoma

Widely used preservative BAK has negative impact on ocular surface and tear-film

Several studies are demonstrating that the long-term administration of preserved topical IOP-lowering drugs, particularly those containing BAK, is associated with ocular toxicity and surface changes.[25,26] Furthermore, it could be shown that there is a correlation between OSD symptoms and the number and duration of glaucoma treatments used.[27,28]

Finally, there are several studies in animals and humans that have shown that BAK (and/or BAK-containing IOP-lowering drugs) affects the ocular surface by decreasing TBUT and tear secretion, decreasing epithelial thickness, leading to degeneration of the cornea epithelium and an increased epithelial permeability. In conjunctival tissues BAK is decreasing the mucin production through a loss of goblet cells, disturbs the integrity of cell membranes and leads to an inflammatory response and apoptosis.

Tear-film osmolarity – an excellent marker for the severity of OSD

Studies are confirming that tear-film osmolarity is an excellent marker for the severity of OSD.[29,30] Osmolarity measures the total of solute concentrations in liquids. The normal osmolarity range of the tear-film in healthy eyes seems to be between 275 and 300 mOsm/L. Hyperosmolarity of the tear-film causes ocular surface cell damage and dehydration with abnormal electrolyte balance is typical in patients with dry eye. In patients with dry eye osmolarity levels are usually above 316 mOsms/L.

Effects of switching medication from preserved Latanoprost to preservative-free Tafluprost evaluated

I. Janulevičienė presented the results of a prospective open-label, observer masked, 3-month study in which the effects on tolerability, tear osmolarity and IOP lowering effect in glaucoma patients switched from BAK containing Latanoprost to preservative-free Tafluprost were evaluated.[31]

30 patients with open-angle glaucoma expressing tolerability disorders with current Latanoprost treatment and/or showing abnormal values of tear osmolarity and/or corneal fluorescein staining and/or abnormal tear-film break-up time (TBUT) were included in the study. IOP was measured by Goldman applanation tonometry, tear-film osmolarity was measured using the TearLab Osmolarity system. Further parameters that were evaluated: TBUT and fluorescein staining of the cornea. All measurements were done at baseline (medical treatment with BAK preserved Latanoprost) and 2,6 and 12 weeks after switching the medication to preservative-free Tafluprost. After baseline visit and after the final visit subjective symptoms of the study participants were evaluated using the Ocular surface disease index questionnaire (OSDI) and the Ocular surface symptoms in glaucoma scale (OSSG)

After 12 weeks significantly less patients complained about ocular symptoms (Figure 7). TBUT increased and the number of patients with abnormal values for corneal fluorescein staining decreased both significantly until week 12. Mean tear-film osmolarity decreased significantly from baseline (315 mOsm/L) until week 6 (302 mOsm/L) and remained unchanged until week 12 (302 mOsm/L). Tear-film osmolarity decreased in 57% of all eyes two weeks after changing medication to preservative-free Tafluprost. (Figure 8).

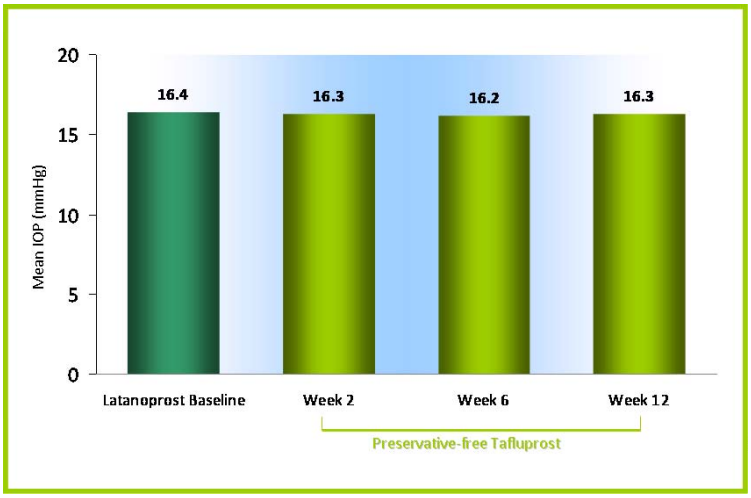


Figure 7: Mean IOP in patients switched from BAK preserved Latanoprost to preservative-free Tafluprost

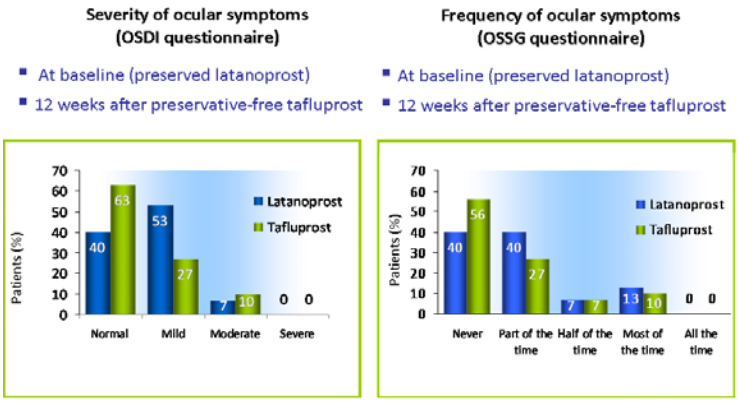


Figure 7: Development of severity and frequency of ocular symptoms

SUMMARY AND CONCLUSIONS

- **Prevalence of OSD in patients with glaucoma and ocular hypertension is very high and should be considered in the medical treatment of glaucoma**
- **Glaucoma medications – especially those containing the preservative BAK are associated with ocular toxicity and changes of the ocular surface**
- **Tear-film osmolarity is an excellent marker for measuring the severity of OSD**
- **After switching patients from preserved Latanoprost to preservative-free Tafluprost ocular signs and symptoms improved significantly**
- **IOP remained unchanged after the switch to preservative-free Tafluprost**
- **Tear-film osmolarity decreased significantly after the change from the BAK preserved Latanoprost to the preservative-free Tafluprost**

- After 2 weeks tear-film osmolarity reduced in 57% eyes ($p<0.005$; t test)
- After 3 month tear-film osmolarity reduced in 83% eyes ($p < 0.001$; t test)

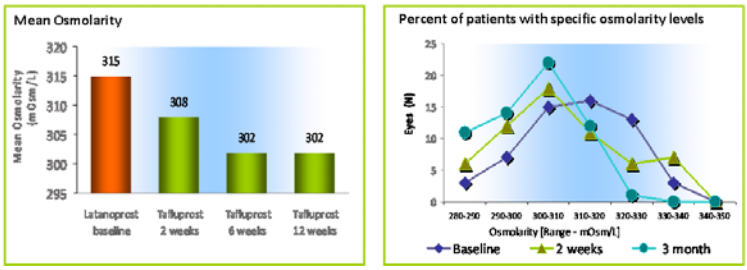


Figure 8: Changes in tear-film osmolarity after switch to preservative-free Tafluprost

Innovation in the treatment of dry eye with cationic emulsion (Novasorb® technology)

In the final talk Jean-Sébastien Garrigue, Director of Research & Development at Novagali Pharma, a Santen Group Company presented an innovative approach for the treatment of symptoms of dry eye, the Novasorb® technology. This technology is a unique cationic nano-emulsion.

Emulsions are mixtures of two liquid or semi-liquid substances that do normally not mix such as oil and water. The first emulsions used in ophthalmology were developed in the early 90's by Benita et al. in order to improve the delivery of lipophilic drugs such as cyclosporine, steroids and other compounds and later as moisturing and lubricating agents. These emulsions were negatively charged using phospholipids as emulsifiers. The major concept behind the development of cationic emulsions for ophthalmic use is to achieve an electrostatic attraction between the positively charged nano-particles of the emulsion and the negatively charged surface of the eye. (Figure 9) The droplet-size of the Novasorb® nano-emulsion is about 150 nm which means that several billions of droplets are included in just one drop of the nano-emulsion, Cationorm®.

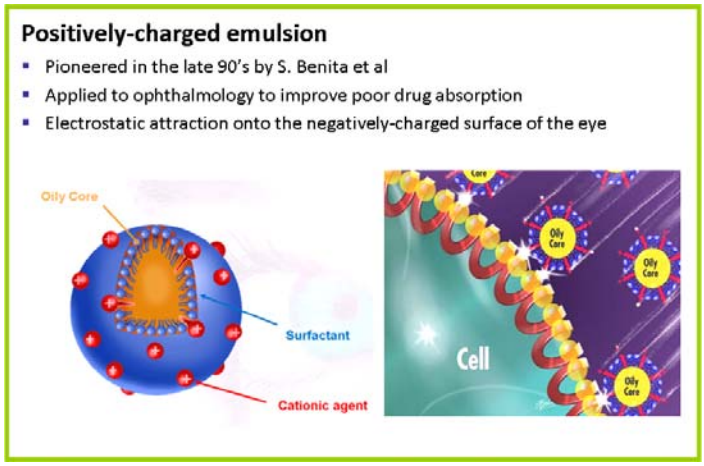


Figure 9: Novasorb® - Cationic oil-in-water nano-emulsion

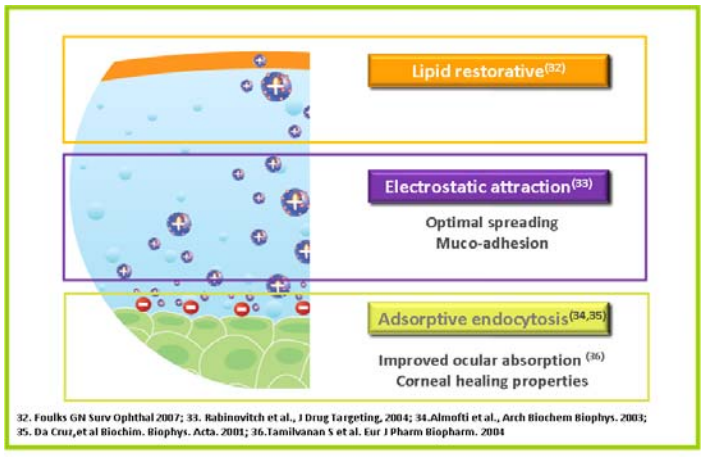


Figure 10: Novasorb® - Interactions with tear-film layers

J.S. Garrigue highlighted the latest developments in the treatment of dry eye symptoms: The Novasorb® technology.

Cationorm® is safe and comparable to natural tears

Toxicity studies showed that Catonorm® is as safe as a saline solution. It was also investigated how Cationorm® interacts with the natural tear-film: A part of the nano-droplets interact with the lipid layer of the tear-film showing a restoring effect stabilizing the tear-film which leads to protection from evaporation. However, most of the positively charged droplets are undergoing electrostatic attraction by the negatively charged cornea epithelium (Figure 10).

Comparison of Cationorm® with Carboxy-Methylcellulose in dry eye patients

J.S. Garrique presented the data obtained in two clinical studies: In the first study Cationorm® was compared to Carboxy-Methylcellulose (CMC), in the second study the comparator was Hyaluronic acid. In the study comparing the new nano-emulsion with CMC patients 46 patients with dry eye were randomized to receive either Cationorm® or CMC 0.5%. Before treatment and application of the first drop patients were asked to fill an OSDI questionnaire, TBUT, Inter-blink index (IBI) and Ocular protection Index (OPI) were determined. After the application of the first drop all parameters, excluding the OSDI were collected again. Patients were then treated over a time period of 2 weeks with their dry eye medication using 4 drops per day. After 1 and 2 weeks patients were re-examined and all parameters were assessed. Clinical signs such as TBUT increased significantly within 1 hr after the first instillation of Cationorm® - significantly more than in the patient group treated with 0.5% CMC.

Increase of TBUT in the patient group treated with Cationorm® further continued until the final visit after 2 weeks. Severity of dry eye symptoms decreased from severe to mild in the patient subgroup treated with Cationorm® and from severe to moderate in the patient subgroup treated with CMC 0.5% as evaluated with the OSDI.

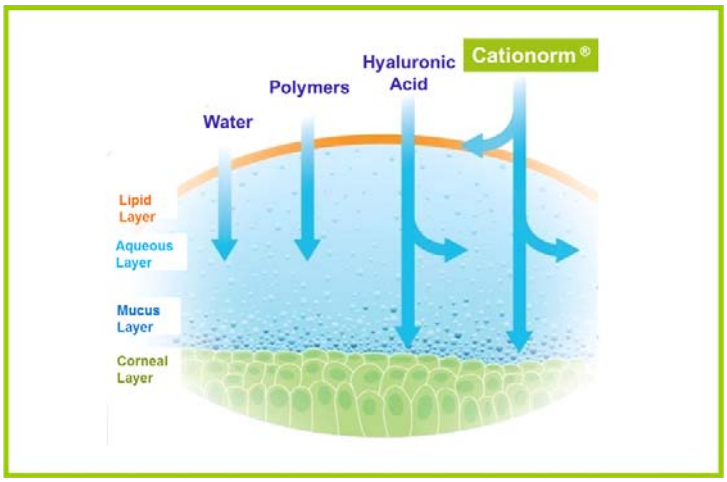


Figure 11: Use of cationic emulsion for dry eye relief

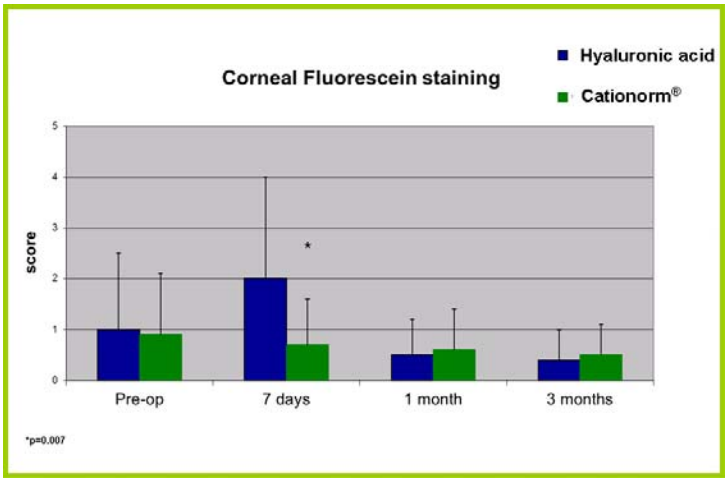


Figure 12: Recovery of the cornea epithelium after PRK

SUMMARY AND CONCLUSIONS

- **Cationic nano-emulsions have unique properties in the treatment of OSD: They show a rapid and smooth spread over the eye and mimic and stabilise all three layers of the natural tear-film**
- **Cationic nano-emulsions are safe and comfortable to use**
- **Patients with dry eye and patients that were treated post PRK with the nano-emulsion (Cationorm®) showed a fast and long-lasting relief of ocular signs and symptoms**
- **The nano-emulsion technology may be beneficial to be used as a vehicle for lipohilic compounds in order to achieve a better penetration and longer retention**

Comparison of Cationorm® with Hyaluronic acid in patients post PRK

Efficacy and tolerability of the cationic nano-emulsion were also evaluated in the recovery post PRK in 40 patients (80 eyes). In this controlled, randomized, multi-center, single-masked study Cationorm® was compared to hyaluronic acid 0.2% after bilateral PRK done with myopic subjects. Follow-up visits were scheduled 7, 30 and 90 days after the refractive surgery. The clinical endpoints of this study were the re-epithelialization of the cornea, TBUT, Schirmer's test and staining of cornea and conjunctiva with fluorescein. In addition subjective symptoms such as pain, photophobia, foreign body sensation and ocular dryness were evaluated. Figure 12 shows the results of this study with respect to fluorescein staining of the cornea. Before the refractive surgery cornea staining was comparable to a 'none to mild' keratitis. 7 days after the PRK corneal staining increased significantly in the patient group treated with hyaluronic acid and remained unchanged in the Cationorm® subgroup.

Subjective symptoms such as eye pain, photophobia, foreign body sensation and ocular dryness improved fast after the refractive surgical procedures in the Cationorm® subgroup of patients. The improvement seemed to be faster compared to the hyaluronic acid treated subgroup of patients (Figure 13).

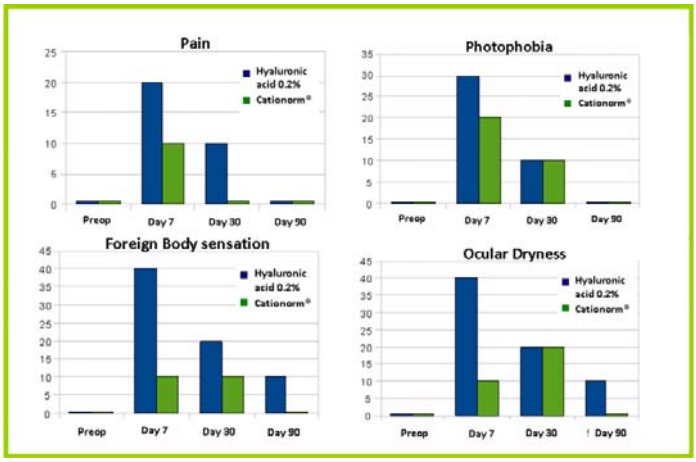


Figure 13: Development of subjective symptoms post PRK

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