

Surface Anaesthesia for Cataract Surgery

a report by

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Surface anaesthesia for cataract surgery was first employed at the end of the 19th century, shortly after discovering the pharmacological properties of cocaine. Thereafter, surgeons turned to retrobulbar anaesthesia with injections, as pioneered by Atkinson. This remained the standard approach for more than 80 years. Modern surface anaesthesia in cataract surgery began in 1991, when Fichman performed a series of phacoemulsifications under topical anaesthesia using 0.5% tetracaine eye-drops. The technique spread rapidly and other drugs were tested with good results. This showed that surface anaesthesia was an effective and repeatable technique – safer than retrobulbar or peribulbar injections. In addition, the intraocular irrigations of anaesthetic agents to improve analgesia were postulated in 1993. The first results on large series of patients were published in 1997.

Pharmacological and Surgical Background

Ocular sensitivity is based on terminations of the fifth cranial nerve, especially those that distribute to the cornea and to the ciliary body in the anterior part of the eye. These fibres are generally non-myelinated – types A-delta and C. They are able to carry sensation of pain, temperature and touch and (in comparison with motor fibres) are blocked by a lower concentration of drugs. As would be expected, ocular sensitivity decreases under low temperatures and with age. Owing to the fact that pain sensation reflects the number of nerves involved rather than the depth of the injury, corneal abrasions are by far more painful than corneal penetrations. To suppress pain, sensitive nerves have to be blocked by anaesthetic agents. The block can take place along the nerve itself or at its sensory terminations. Nerve block is commonly achieved in local anaesthesia by drug injection. The most important component of surface anaesthesia is blocking the nerve at its sensory terminations. This involves the inhibition of sodium channels at nerve endings or receptors by the anaesthetic agents. It is therefore the production (and not the transmission) of the nervous impulse that is blocked.

Anaesthetics applied topically to the eye act directly on the corneal epithelium and stroma. It is the part of the

drug penetrating into the anterior chamber that suppresses iris and ciliary body pain. The amount of drug reaching deep set structures can be increased by repeating eye-drop applications before surgery starts or by further applications after the first surgical incisions, i.e. additional eye-drops may be applied after conjunctival incision or intracameral injection after opening the anterior chamber. The duration of the effect of topically applied anaesthetics depends on the properties of the drug used. For commonly used agents the effect usually lasts between 15 and 20 minutes, but eye-drop instillations or intracameral irrigations can be repeated at intervals during surgery if required. Motor fibres are blocked only if high drug concentration is achieved. The intraocular muscles are affected by topical/intracameral anaesthesia (producing mydriasis), but there is no way of blocking extraocular muscles or obtaining akinesia of the eyeball.

The absence of ocular akinesia makes small incision surgery mandatory. In phacoemulsification for cataract surgery, two incisions are made with the main incision not exceeding 3.2mm. This allows the surgeon to stabilise and to direct the eye with two instruments. In glaucoma surgery, incisions no wider than 4mm are preferred for trabeculectomy. The retained ocular motility can be useful to the surgeon during the operation, if the patient is able to follow simple instructions. During surgery, instruments are moved as levers through the incisions, thus directing the globe, improving stability, preventing fluid leakage with intraocular pressure variations and performing surgical manoeuvres. In cataract surgery, careful hydro-dissection prevents excessive ciliary body stimulation by zonular fibres during nucleus rotation. During surgery, the use of cold irrigating solutions can decrease ocular sensitivity. In addition, in modern cataract and glaucoma surgery, painful manoeuvres such as muscle sutures, conjunctival and iris manipulation, diathermy and tissue sutures are limited. The advantages of topical anaesthesia over periocular injections include not only a higher safety level, but also increased analgesia consistency during surgery and lower intraocular pressure. Moreover, the limited level of drugs employed inhibit the general side effects commonly observed with local anaesthesia. The return of sensitivity soon after surgery allows

immediate detection of any unexpected ocular pain that might suggest complications.

Drugs Employed

From a pharmacological point of view, surface anaesthetics employed in ophthalmology are tertiary amines composed of an aromatic hydrophobic ring (usually benzene) and an amidic hydrophilic group, with an ester (proparacaine, tetracaine or benoxinate) or an amidic (lidocaine, etidocaine, mepivacaine or ropivacaine) intermediate chain. The properties of the drug – potency, onset, duration of action and selectivity – are determined by the chemical configuration of the two ends of the molecule. Generally, the ester-bound compounds have a faster and shorter action than the amide-bound compounds. The anaesthetic agents useful in clinical practice are unstable in their amine form and insoluble in water. They are therefore prepared as salts that are stable in solution at relatively acid pH. The low pH of commercially available solutions is the main cause of the burning sensations perceived on the first application of eye-drops. After topical application in the conjunctival sac, the compounds have to obtain the non-dissociated form to cross the tear film and the cornea, and to return to the dissociated form at nerve endings or axons to exert the anaesthetic activity. The

chemistry of body fluids and the activity of tissue enzymes favour these passages. The ester compounds are rapidly hydrolysed by plasmatic esterases, and to a smaller extent by tissue esterases. The amide compounds are degraded more slowly, mainly in the liver rather than the eye. They are therefore active for a longer period of time (see *Table 1*).

The amide-bound lidocaine is probably the most often employed surface anaesthetic in ophthalmic surgery. It is certainly the most employed for intracameral irrigations. It is available in concentrations of 1% to 4% with the unpreserved preparation being preferred for increased local tolerability. The instillation is rather painful as the pH of the solution is usually lower than six. With regards to intraocular penetration, Zehetmayer et al. found a high dependence on the solution pH, as would be expected from the chemical properties. Behndig and Linden measured the lowest aqueous humour levels to be found in published investigations. Higher levels were found by the author following repeated instillations. This was probably because damage to the corneal surface favoured penetration. The correlation discovered between lidocaine levels in aqueous humour and pain scores was not confirmed by Bardocci et al. Intraocular penetration of topically applied bupivacaine has been studied by Lagnado et al. Following three or six



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Presentation: Oftaquix® 5 mg/ml eye drops. One ml of eye drops solution contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg of levofloxacin. Clear, light yellow to light greenish-yellow solution, practically free of visible particulate matter. **Therapeutic indications:** Oftaquix® 5 mg/ml eye drops are indicated for the topical treatment of bacterial external ocular infections in patients 1 year of age caused by levofloxacin susceptible microorganisms. Considerations should be given to official guidance on the appropriate use of antibacterial agents. **Posology:** For all patients instill one to two drops in the affected eye(s) every two hours up to 8 times per day while awake for the first two days and then four times daily on days 3 through 5. If different topical ocular medications are used concomitantly, at least a 15-minute interval is required between instillations. To prevent contaminating the dropper tip and solution, the dropper tip should not come into contact with the eyelids or surrounding areas. While Oftaquix® 5 mg/ml eye drops have been administered for up to 15 days in a safety study, the usual treatment duration is 5 days. The duration of treatment depends on the severity of the disorder and on the clinical and bacteriological course of infection. Safety and efficacy in the treatment of corneal ulcer and ophthalmia neonatorum has not been established. **Contra-indications:** Hypersensitivity to the active substance levofloxacin, to other quinolones or to any of the excipients, e.g. benzalkonium chloride. Oftaquix® 5 mg/ml eye drops must not be given during pregnancy and lactation. **Special warnings and special precautions for use:** Oftaquix® 5 mg/ml eye drops must not be injected sub-conjunctivally. The solution should not be introduced directly into the anterior chamber of the eye. Systemic fluorquinolones have been associated with hypersensitivity reactions, even following a single dose. If an allergic reaction to levofloxacin occurs, discontinue the medication. As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If worsening of infection occurs, or if a clinical improvement is not noted within a reasonable period, discontinue use and institute alternative therapy. Whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining. This formulation of Oftaquix® 5 mg/ml eye drops contains benzalkonium chloride as a preservative and should not be used in patients continuing to wear hydrophilic (soft) contact lenses as the preservative may be absorbed and cause eye irritation.

Generally, patients should be advised not to wear any contact lenses if they have signs and symptoms of bacterial conjunctivitis. **Interaction with other medicinal products and other forms of interactions:** Specific drug interaction studies have not been conducted with Oftaquix® 5 mg/ml eye drops. Since maximum plasma concentrations of levofloxacin after ocular administration are at least 1000 times lower than those reported after standard oral doses, interactions mentioned for systemic use are unlikely to be clinically relevant when using Oftaquix® 5 mg/ml eye drops. If different topical ocular medications are used concomitantly, at least a 15-minute interval is required between instillations. **Pregnancy and Lactation:** Administration of Oftaquix® 5 mg/ml eye drops during pregnancy and lactation is contra-indicated as tyrosine inhibitors have been shown to cause growth disorders of weight bearing joints in animal studies. As yet, the plasma concentrations of levofloxacin reached after application to infected eyes are not known. **Undesirable effects:** Approximately 10% of patients can be expected to experience adverse reactions. The reactions are usually graded as mild or moderate, are transient, and are generally restricted to the eye. As the product contains benzalkonium chloride, contact eczema and/or irritation may be due to the active component or to this preservative. **Common adverse reactions (1% to 10% of patients):** Ocular burning (1.6%), decreased vision (1.2%) and mucous strand (1.2%). **Uncommon adverse reactions (0.1% to 1% of patients):** Lid matting (0.9%), chemosis (0.7%), conjunctival papillary reaction (0.7%), lid oedema (0.5%), ocular discomfort (0.5%), ocular itching (0.5%), ocular pain (0.5%), conjunctival injection (0.2%), conjunctival follicles (0.2%), ocular dryness (0.2%), lid erythema (0.2%) and photophobia (0.2%). Other reactions observed in the clinical studies included headache (0.1%) and rhinitis (0.1%). No corneal precipitates were observed in clinical studies. **Overdose:** The total amount of levofloxacin in a bottle of eye drops is too small to induce toxic effects after an accidental oral intake. If considered necessary, the patient can be observed clinically and supportive measures can be undertaken. After a local overdose with Oftaquix® 5 mg/ml eye drops, the eyes can be flushed with clean [tap] water at room temperature. **Shelf life:** 3 years. After first opening to be used within 28 days. **Marketing authorisation holder:** Santen Oy, Niityhänkatu 20, 33720 Tampere, Finland. **Marketing Authorisation Number(s):** PL 16058/0006

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Table 1: Agents Employed for Surface Anaesthesia in Ophthalmic Surgery

Agent	Concentration (eye-drops)	Action onset (min)	Duration (min)	pH	pKa (25°C)	% base (pH 7.4)
Amide Compounds						
Lidocaine	4.0%	2–5	15–20	6.0–6.5	7.9	25
Bupivacaine	0.5–2%	5–10	20–30	4.5–6.0	8.1	15
Ropivacaine	1.0%	2–5	15–20	5.0–6.5	8.1	15
Mepivacaine	2%	1–3	10–15	5.5–6.0	7.6	40
Ester Compounds						
Tetracaine	0.5%	0.5	10–15	4.5–6.5	8.5	15
Proparacaine	0.5%	0.25	5–10	5.0–6.0	3.7	75
Benoxinate	0.4%	0.25	5–10	5.0–6.0	2.2	80

The low pH of the instilled solution is associated with subjective burning on application.

If the pKa is high, the molecule is more dissociated at physiologic pH (low % base at pH 7.4) with higher surface activity but poorer corneal penetration.

instillations, they found that the number of instillations was not related to the intraocular level of bupivacaine, nor to pain scores.

General side effects and the potential risks of needle injections are avoided with surface anaesthesia, although local side effects may still occur. The inhibition of cellular sodium channels may cause some swelling of the corneal epithelium, particularly in older patients, with the possibility of superficial punctate keratitis. When preservatives are added to the solution, epithelial toxicity is even more pronounced. The anaesthetic interruption of the blinking reflex increases this local toxicity and suggests it could be beneficial to close patients' eyes after bilateral instillation. These epithelial side effects can reduce corneal transparency during surgery, favouring the reduction of eye-drop instillation and the addition of intracameral anaesthetic irrigation. The toxicity may linger for a few days after surgery, often slightly affecting vision in both eyes where bilateral instillation has taken place. Some of the authors' patients reported dry eye sensations in the contralateral eye (i.e. the eye that had not been operated on), lasting eight to 12 weeks after surgery that had not been experienced following retrobulbar block. In approximately one in 1,000 patients, the burning sensation lasted more than one year and could be considered permanent.

Intracameral Drug Irrigation

Intracameral irrigation of anaesthetic agents, first proposed by Gills et al., is employed by over 70% of surgeons adopting surface anaesthesia. The intraocular irrigation of diluted anaesthetics is usually performed either immediately after the first corneal incision or at hydrodissection, but can be repeated in prolonged or complicated surgeries.

The most frequently employed drug is lidocaine at 1% concentration, probably because of its simplicity in preparation, although other drugs have been tested for intracameral irrigation. Lidocaine 1% is mainly

prepared at the time of surgery from 4% solutions by dilution with the usual balanced salt solution employed for intraocular irrigations. The pH and intermixture of the injected solutions should be checked at intervals.

Within the anterior chamber, a part of the drug is rapidly absorbed by the surrounding anatomic structures (iris, ciliary body and cornea), while the drug still present in the solution is removed by subsequent anterior chamber irrigations; tissue exposure is therefore limited. Anterior chamber levels of the drug are 100 times more elevated than after the application of eye-drops. Behndig and Linden found these levels to be 341.8µg/ml ± 151.6µg/ml and Wirbelauer et al. found similar results.

With intraocular irrigations, there is some concern about the possibility of permanent corneal or retinal damage. The safety of intracameral irrigations with anaesthetic agents has been studied extensively, beginning with amaurosis, which was encountered in some patients after posterior capsule rupture. Initial animal studies showed no permanent toxicity and these were followed by clinical studies on human cornea, retina and optic nerves that confirmed the safety of lidocaine and mepivacaine. Other compounds, such as bupivacaine, could be more toxic.

Variations in Drug Preparation

Single applications of the gel preparations of anaesthetic agents have been employed to prolong the contact between the drug and ocular surfaces. These are as effective as repeated eye-drop instillation in providing anaesthesia for cataract surgery. Lidocaine has been the most employed agent, but tetracaine was also found to be effective. The advantages of using gel preparations over eye-drop instillations include less burning on application and less corneal dehydration. ■

This article is continued, with references and an additional table, in the Reference Section on the website supporting this business briefing (www.touchbriefings.com).