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REVIEW

A novel lidocaine hydrochloride ophthalmic gel for topical ocular anesthesia

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HR Shah[1]
E Reichel[2]
BG Busbee[3]

[1]New England Eye Center Boston, MA, USA; [2]Vitreoretinal Service, New England Eye Center/Tufts University School of Medicine, Boston, MA, USA; [3]Tennessee Retina, Nashville, TN, USA

Abstract: Topical anesthetics play an important role in the practice of ophthalmology, both for procedures in the office and in the operating room. The need for safe, long-acting topical ocular anesthetic agents is ongoing, and has been highlighted by the increase of intravitreal administration of pharmacologic agents. Current practices for ocular anesthesia include subconjunctival injection of 2% aqueous lidocaine, topical 2% lidocaine drops and topical 0.5% tetracaine. Tetracaine is not yet FDA approved, and is associated with corneal epithelial toxicity and delayed epithelial healing after multiple administrations. Lidocaine jelly (2%) preparations have been reported to be beneficial in several systemic procedures, including those of the upper airway, dental, urogenital, and gastrointestinal. It has been theorized, and recent studies support the idea, that gel formulations of lidocaine may enhance anesthetic effect, and therefore be superior to anesthetic solutions for topical cataract surgery. The viscous nature of gel formulations is thought to lengthen contact time, resulting in better anesthesia at lower drug concentrations. Furthermore, several studies suggest that lidocaine is bactericidal and bacteriostatic, and may have a supplementary role in preventing and treating surgical site infections. Akten™, lidocaine 3.5% gel (Akorn, Buffalo Grove, IIlinois) was FDA approved for all ophthalmic procedures in October 2008. This gel is a preservative-free, lidocaine-based anesthetic gel consisting of 35 mg/mL of lidocaine hydrochloride. We describe the properties, including chemical structure, indications, evidence of support, use, adverse effects, and precautions, which we believe enable Akten to provide superior anesthesia, while minimizing side effects.

Keywords: Akten, lidocaine gel, topical anesthetic, ocular surgery

Introduction/background

Topical anesthetics play an important role in the practice of ophthalmology, both for procedures in the office and in the operating room. Until October 2008, the only Food and Drug Administration (FDA)-approved topical anesthetic preparation for ocular procedures was proparacaine. It is only available in solution form. Furthermore, its drop formulation typically requires repeated applications to achieve adequate surface anesthesia and often adjunctive intracameral injection of lidocaine solution is necessary for achieving adequate anesthesia for intraocular procedures. Tetracaine is another topical anesthetic frequently used for topical anesthesia in ophthalmology. It is not FDA-approved, and is known to be associated with corneal epithelial toxicity and delayed epithelial healing after multiple administrations. Topical ophthalmic anesthetic preparations are typically acidic, which contributes to the stinging sensation when first applied.

Ocular anesthesia can be delivered by a variety of routes. This includes retrobulbar and peribulbar injection, sub-Tenon's injection, subconjunctival injection, intracameral

Correspondence: Brandon G Busbee
Tennessee Retina, 345 23rd Ave N, Suite 350, Nashville, TN 37203, USA
Email bgbusbee@yahoo.com

injection and topical application. The vast majority of ophthalmic procedures are performed using topical anesthesia. Minimizing the use of needles and invasive techniques to deliver anesthesia has been an ongoing trend in ophthalmic anesthesia over the past decade.

Recent practices for ocular anesthesia involving an intravitreal injection include subconjunctival injection of 2% aqueous lidocaine, topical 2% lidocaine drops and topical 0.5% tetracaine. The technique for 2% subconjunctival lidocaine has been described in a multicenter, randomized trial;[1] however, the FDA has not yet approved for this indication.

Lidocaine jelly (2%) preparations have been reported to be beneficial in upper airway,[2,3] dental,[4] urogenital,[5] and gastrointestinal procedures.[6] The use of lidocaine topical anesthetic as a single agent for ocular procedures has been reviewed in several studies.[7–13] Although considered an off-label use of lidocaine 2% (urogenital) jelly, many of these ophthalmic studies had positive findings. It has been theorized, and recent studies support the idea, that gel formulations of lidocaine may enhance anesthetic effect, and therefore, be superior to anesthetic solutions for topical cataract surgery.[7–10] The viscous nature of gel formulations is thought to lengthen contact time with pain-sensitive ocular structures, resulting in better anesthesia at lower drug concentrations. In fact, a pilot study demonstrated superior anesthetic efficacy of adjunctive lidocaine gel with retrobulbar anesthesia for 25-gauge vitrectomy.

Several studies, dating back to the 1970s, suggest that lidocaine is bactericidal and bacteriostatic, and may supplement in preventing and treating surgical site infections. More recently, Parr et al demonstrated that clinical doses of lidocaine in surgical site infections inhibited the growth of *Escherichia faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MSRA), and vancomycin-resistant enterococci in a dose-dependent fashion.[14] In a guinea pig model, Stratford et al evaluated the benefit of lidocaine on bacterial colonization of surgical wounds by comparing two wounds on each animal. One was infiltrated with lidocaine 2%, and the other left untreated. Results showed a >70% decrease in colony counts in the wound treated with lidocaine.[15] Overall, lidocaine has been proven to be effective against *Candida albicans*, *E. coli*, *E. faecalis*, *Haemophilus influenzae*, MRSA*, S. aureus*, *Staphylococcus epidermidis*, *P. aeruginosa*, *Streptococcus pneumoniae.* Concentrations of lidocaine that are greater than 2% (and up to 5%) can be effective in stopping bacterial growth.[16–18]

The need for safe, long-acting topical ocular anesthetic agents is an ongoing need for ophthalmology practices. This has been highlighted with the adoption of intravitreal administration of pharmacologic agents for many retina vascular diseases. In short, there has been an explosion in the number of intravitreal injections in the past few years, with some one million injections being performed annually. Intravitreal injections are done in the office setting and are most commonly done with topical anesthesia. Other retinal procedures requiring longer-acting topical anesthetic agent include panretinal photocoagulation, focal laser coagulation, laser retinopexy in the treatment of retinal tears, cryotherapy of retinal tears and detachments, and vitreoretinal surgery. Many surgical procedures are also done using topical anesthetic agents, including cataract surgery, glaucoma filtration surgery, anterior segment lasers, and strabismus surgery.

Herein we describe the lidocaine 3.5% gel (Akten™; Akorn, Buffalo Grove, Illinois, USA) that was FDA-approved for all ophthalmic procedures in October 2008. This gel is a preservative-free lidocaine-based anesthetic gel consisting of 35 mg/mL of lidocaine hydrochloride. The preparation is pH neutral. The gel contains hydroxypropylmethyl cellulose, allowing for extended corneal and conjunctival contact, which has been demonstrated to provide effective topical anesthesia. Furthermore, the viscous solution likely preserves exposed epithelial surfaces. Akten also has the benefit of being 50% less viscous compared to non-ophthalmic gel allowing for drop application. These properties of Akten impart numerous advantages in its use for ophthalmic procedures. The reduced viscosity of lidocaine 3.5% gel, relative to lidocaine 2%, also allows for the preparation to be easily washed off of the eye so that debris and bacteria do not remain trapped beneath the viscous vehicle. This provides a potential advantage against intraocular infection that was not possible with the lidocaine 2% off-label jelly.[19] The lower viscosity lidocaine 3.5% gel also maintains a homogeneous, regular surface allowing for unimpaired observation of anterior segment and retinal structures, so important for performing intraocular procedures. These properties of Akten 3.5% gel have been shown to result in less epithelial irregularities and toxicity than topical anesthetic solutions that do not contain hydroxypropylcellulose.[10,20]

Chemical structure

The active ingredient is lidocaine hydrochloride, an amino amide-type local anesthetic, first synthesized by Swedish chemist Nils Lofgren in 1943, and marketed in 1949. It is prepared by first reacting 2, 6-xylidine with chloroacetyl

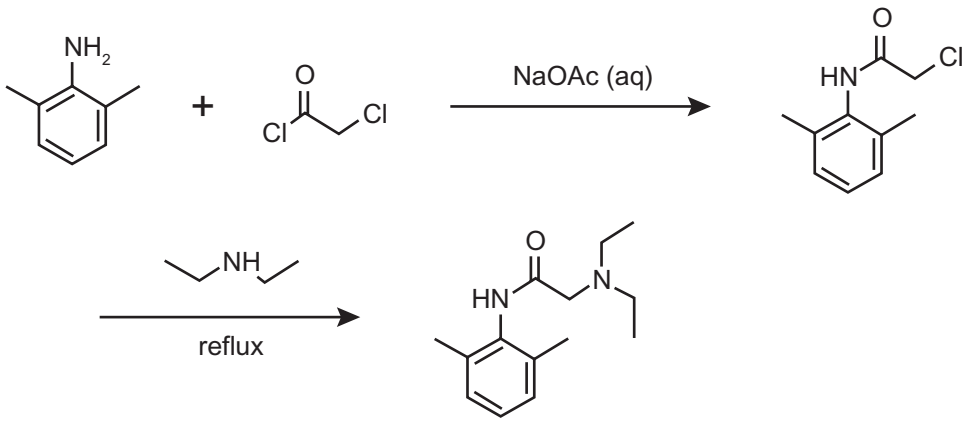

Figure 1 Synthesis of lidocaine.

chloride, and then by a reaction with diethylamine (see Figure 1).[21] It is designated chemically as acetamide, 2-(diethylamino)-N-(2, 6-dimethylphenyl) monohydrochloride with a molecular formula of C14H22N2O HCl and molecular weight of 270.8.

Lidocaine hydrochloride acts by stabilizing the neuronal membrane by blocking the fast voltage gated sodium (Na^+) channels, preventing the postsynaptic neuron from depolarizing. This affects local anesthetic action by failing to transmit an action potential.[22]

The plasma binding of lidocaine is dependent on drug concentration and the fraction bound is inversely proportional to the concentration. At concentrations of 1 to 4 μg/mL of free base, 60% to 80% of lidocaine is protein bound. Lidocaine is 90% metabolized in the liver.

Indication/rationale/evidence of support use

A pivotal prospective, randomized, double-blinded, multicenter Phase III clinical trial demonstrated the efficacy of lidocaine 3.5% gel. This study led to FDA-approval of Akten in 2008. Eight study centers participated in this trial. A total of 209 subjects were enrolled with 54, 51, 53, and 51 subjects randomized to the sham, lidocaine 1.5% gel, lidocaine 2.5% gel, lidocaine 3.5% gel groups, respectively. Patients were evaluated for efficacy and safety of all of the lidocaine gel preparations. Anesthesia was determined to be present if there was an absence of pain after pinching the conjunctiva with 0.3-mm forceps. Anesthesia was achieved within 5 minutes of application in 92% of the subjects. Of this group, 87% achieved anesthesia within 1 minute. The mean time to anesthesia onset was not affected by the dose. Anesthesia generally occurred between 20 seconds to 1 minute and persisted for 5 to 30 minutes. The mean time to anesthesia onset in the clinical study was 60 seconds, with a median onset time of 40 seconds. The duration of anesthesia ranged from 5 minutes to 40 minutes, with mean anesthesia duration of 13.4 minutes. Akten 3.5% provided a longer duration of approximately 15 minutes.[20]

Page et al recently evaluated the use of lidocaine hydrochloride ophthalmic gel in a literature review of 25 studies, including 15 prospective randomized controlled trials (RCT),[7,8,11,20,23–33] 6 nonrandomized prospective studies, 2 animal studies, 1 microbiologic study, and 2 letters to the editor. Data from the 15 prospective RCTs are summarized in Table 1.[34] Two of these were double-blinded, of which one was the previously described Akten clinical trial.[7,20] The 15 RCTs included a total of 933 patients. Five of the 13 RCTs, including the randomized trial of Akten, revealed a statistically significantly lower pain score in the lidocaine gel group compared with other modalities of ocular anesthesia. Five RCTs compared the requirement for additional anesthetic applications for patient comfort,[8,11,23,24,32] and 4 of these demonstrated that lidocaine gel resulted in a statistically significantly lower number of supplemental anesthetic applications.[8,11,23,24] Two papers found significantly higher intracameral lidocaine levels in those receiving lidocaine gel than lidocaine drops.[7,12] In this review of ocular anesthesia, only the Akten trial described time to onset and duration of anesthesia in detail.[20] Several studies evaluated surgeon and patient satisfaction. Soliman et al reported that 93.3% of patients reported satisfaction undergoing cataract surgery with lidocaine jelly versus 83.3% of those who received bupivicaine drops.[8] In an another small study, Segev et al reported that 14 of 15 patients preferred the lidocaine jelly over previous experience of retrobulbar injection during penetrating keratoplasty.[35] In conclusion, the series of papers compared in the usage of lidocaine gel suggests it is often

Table 1 Summary of prospective randomized controlled trials comparing lidocaine gel with another anesthetic modality[34]

Author	N	Product tested	Procedure	Control	Endpoint	Secondary measure	*P* value
Busbee et al[20]	209	Akten 1.5%/2.5%/3.5%	Conjunctival pinching with 3 mm forceps	Sham gel	Pt reported anesthesia within 5 minutes: 88% of subjects (Akten 1.5% group)/89% (Akten 2.5% group)/92% (Akten 3.5% group)/22% (sham)	Duration of anesthesia: 10.2 min (Akten 1.5%)/11.7 min (Akten 2.5%)/13.4 min (Akten 3.5%)/2.8 min (sham)	<0.001 for all groups vs sham
Barequet et al[23]	25	Lidocaine gel 2%	Cataract extraction	Tetracaine drops	Cochet-Bonnet esthesiometer (score 0–6, 0 = total anesthesia, 6 = pain): before instillation, 5 minutes post instillation, post surgery. Lidocaine group: 6/0/0. Tetracaine drops group: 5/0/0	Need for additional drops (17% gel group vs 31% drops group)	<0.01 (need for additional drops)
Young et al[24]	40	Lidocaine gel 2%	Primary pterygium excision + MMC	Tetracaine drops + solcoseryl eye gel	VPS (0–10): during and after surgery. No sig difference between groups except during conj closure [0.47 ± 0.84 (gel group) vs 1.43 ± 1.66 (tetracaine drops group)]	No of additional drops needed (0.16 ± 0.11 vs 0.67 ± 0.09)	<0.03 (pain), <0.001 (need for additional drops)
Theocharis et al[25]	69	Lidocaine gel 2%	25 g and 23 g sutureless vitrectomy	Peribulbar anesthesia	VAS pain scale, intraoperative and postoperative. No stastically significant difference in pain between groups	Surgeon-reported "ease of surgery" under topical conditions (0–10 scale): (23 g easier than 25 g, $P < 0.001$)	= 0.3 (pain)
Friedman et al[26]	100	Lidocaine gel 2%	Intravitreal injection (30 g)	Subconj lidocaine 2%	VAS pain scale, masked. No sig difference in pain between groups	None	= 0.1 (pain)
Oksuz et al[27]	45	Lidocaine gel 2%, applied regularly in post op period	Primary pterygium excision, post-op	Artificial tear gel, applied regularly in postop period	VAS pain scale: 4th hour post surgery: 4.13 ± 1.86 (lidocaine gel) vs 6.50 ± 1.47 (artificial tear gel); 10th hour post surgery: 2.39 ± 0.89 vs 3.63 ± 1.00	Mean corneal re-epithelialization time (no sig difference)	<0.001 (post op pain)
Kozak et al[28]	16	Lidocaine gel 2%	Intravitreal injection (27.5 g)	Subconj lidocaine 2%	VAS pain scale, masked. No sig difference in pain between groups	None	= 0.82
Thill et al[29]	39	Lidocaine gel 2% + intracameral lidocaine 1%	Cataract extraction	Bupivacaine 0.5% + oxybuprocaine + diclofenac × 4 drops	VAS pain scale, significantly lower pain scores reported in lidocaine gel group	None	<0.001
Oksuz et al[33]	54	Lidocaine gel 2%	Primary pterygium excision + autograft	Subconj lidocaine 2%	VAS pain scale. Pain during administration: 0.92 ± 0.56 vs 4.26 ± 1.18. Pain during surgery: 3.96 ± 0.95 vs 4.0 ± 1.01)	None	<0.01, = 0.55
Rebolleda et al[30]	32	Lidocaine gel 2%	Ahmed glaucoma implant	Retrobulbar injection	VAS pain scale. Pain during administration: significantly more in retrobulbar group. Intraoperative pain: no significant difference	Mean duration of surgery: significantly longer in topical group ($P = 0.049$)	<0.0001 (pain with administration), = (0.317 intraop pain)
Soliman et al[8]	90	Lidocaine gel 2%	Cataract extraction	Bupivacaine 0.5%, benoxinate 0.4%	VPS pain scale (0–10). At instillation: 2.97 (gel group)/1.53 (bupivacaine group)/1.03 (benoxinate group). Mean duration of pain at instillation: 25 s (gel)/14 s (bupivacaine)/6 s (benoxinate). Mean VPS during surgery: 1.6 (gel)/4.1 (bupivacaine drops)/7.1 (benoxinate drops)	Incidence of supplemental sub-Tenon's injection: 3.3% (gel group)/10.0% (bupivacaine)/73.3% (benoxinate). Overall pt satisfaction: 93.3%/83.3%/33.3%	<0.001 for all comparison groups

Bardocci et al[7]	107	Lidocaine gel 2%	Cataract extraction	Lidocaine 4% drops	Intraoperative pain (VAS, 0–10) significantly higher in drops group, intracameral lidocaine concentration significantly higher in gel group	Intraoperative blood pressure increases (significantly higher in gtts group). No correlation found between intracameral lidocaine levels and pain score	<0.001 (pain); <0.001 (intracameral lidocaine concentration)
Yu et al[11]	14	Lidocaine gel 2%	Strabismus, bilateral symmetric	Amethocaine 1% in contralateral eye	VPS (0–10) during surgery: 2.6 (gel) vs 5.3 (amethocaine drops). Surgeon perception of patient discomfort (0–10): 3.2 (gel) vs 6.2 (amethocaine)	Mean no of additional drops needed: 0.3 (gel) vs 1.6 (amethocaine)	<0.01 (pain), = 0.02 (need for additional drops)
Li et al[31]	57	Lidocaine gel 2%	Chalazion excision	Subconj lidocaine 2%	VPS (0–100) at application of anesthetic: 5.5 (gel) vs 47.0 (subconj injection). VPS during surgery 48.28 (gel) vs 51.4 (subconj lidocaine)	"fear of injection" (pt reported, scale 0–100) 43.9 (gel) vs 47.7 (subconj injection) ($P = 0.668$)	<0.001 (pain with administration), = 0.679 (intraop pain)
Zabriskie et al[32]	36	Topical anesthesia	Trabeculectomy	Retrobulbar injection	VAS pain scale, intraoperative and postoperative. No stastically significant difference in pain between groups	Supplemental anesthesia required (no sig difference)	= 0.3

Abbreviations: MMC, mitomycin C; Pt, patient; VAS, visual analogue scale; VPS, verbal pain score.

more effective than other anesthesia modalities in the prevention of procedure-related ocular pain.

The dosing strategy for Akten has been described and tailored for the use in intravitreal injections. The following dosing strategy maximizes anesthesia while providing appropriate antiseptic technique. One drop of lidocaine 3.5% gel is instilled on the ocular surface. After 2 to 3 minutes betadine solution is used to clean the ocular surface. Another drop of lidocaine 3.5% gel is then reapplied and allowed to sit on the ocular surface for at least one additional minute. Typically the patient is asked to gently close their eyes during the reapplication. Akten may be reapplied to maintain anesthetic effect. Prior to the intravitreal injection, betadine is reapplied in the area of intended injection.

Akten can be used for procedures that require an extended treatment time. Due to its viscous formulation, systemic absorption through the nasolacrimal system should be reduced, therefore reducing the potential for systemic toxicity.

Procedures that may require more extensive use of topical anesthesia include cataract surgery, trabeculectomy, pars plana vitrectomy, refractive surgery, and suture adjustment after strabismus surgery.

To date approximately 1 million patients have received topical anesthesia using Akten gel. Application of lidocaine 3.5% gel as described above typically results in a pain-free or minimally painful ocular procedure. Prior to the advent, of Akten, topical anesthetic agents included subconjunctival lidocaine and anesthetic-soaked pledgettes for intravitreal injections, and tetracaine preparations. In our experience, patients commonly note a difference in comfort between the currently used lidocaine 3.5% gel and other previously administered topical anesthetic agents. Another benefit of Akten is the vast majority of patients who have anesthesia done with Akten gel do not suffer the corneal epithelial and surface irregularities that typically occur due to the toxic nature of other anesthetic preparations. This eases the post-operative period and reduces the need for artifical tear lubrication and in our experience use of Akten has replaced the need for additional intracameral lidocaine in patients undergoing topical cataract surgery. It is hypothesized that ocular penetration of lidocaine 3.5% gel results in high anterior chamber levels, adequately anesthetizing the iris and ciliary body, preventing intraoperative discomfort. Finally, we have observed a significant reduction in intraoperative pain in patients undergoing pars plana vitrectomy. Although a retrobulbar block is the primary modality for anesthesia, Akten gel applied preoperatively has been demonstrated to significantly

reduce the potential discomfort at the beginning of a pars plana vitrectomy.

Adverse effects

The adverse events demonstrated by the Akten trial revealed an adverse event rate ranging from 2% to 6% across all treatment groups.[21] The most common adverse event was corneal staining. Corneal staining was reported by 6% (3 patients) in the lidocaine 3.5% gel group, and 2% (1 patient) in the sham group. All patients showed resolution of their corneal epithelial changes within 24 hours. Other common adverse events include conjunctival hyperemia (6%) and conjunctival hemorrhage (3%). Both of these findings are likely due to the technique (0.3 forceps pinching of conjunctiva) by which pain was evaluated in the study. No serious adverse events were noted.

Precautions

With regard to use in pregnancy, reproduction studies for lidocaine have been performed in both rats and rabbits. There is no evidence of harm to the fetus at subcutaneous doses up to 50 mg/kg lidocaine in the rat model. This dosage is more than 800-fold greater than the human dose on a body weight basis. There are no well- controlled studies in pregnant women.

In terms of use in nursing mothers, lidocaine is secreted in human milk. The clinical significance of this is unknown. Caution should be exercised when lidocaine preparations are administered to nursing women.

In the pediatric population, lidocaine safety and efficacy has been extrapolated from studies in older subjects and studies in pediatric patients using different formulations of lidocaine.

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration due to delayed wound healing. Topical ocular application of lidocaine 3.5% gel is not expected to result in systemic exposure.

Conclusion

Akten gel, a preservative-free, pH neutral, 3.5% lidocaine-based anesthetic gel, appears to have significant benefits over standard topical ocular anesthetic agents. Its viscous solution allows for prolonged contact time and, therefore, may provide superior anesthesia relative to other topical solutions. Higher dose lidocaine may also protect from bacterial infections and could potentially reduce the risk of intraocular infections relative to other topical anesthetic agents.[16–18] The hydroxypropylcellulose aids in preserving the corneal epithelium after topical anesthesia is applied, serving an added benefit in the aged population in whom most of the ophthalmic procedures are done. With the dramatic rise in intravitreal injections and other ophthalmology procedures comes a need for better topical anesthetic agents. It is believed Akten gel provides superior anesthesia, while minimizing side effects.

Disclosure

Drs Reichel and Busbee have a commercial interest (royalties) in Akten.

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