Intracameral Anesthesia

In Vitro Iris and Corneal Uptake and Washout of 1% Lidocaine Hydrochloride

Nicole J. Anderson, MD; Wendell D. Woods, PhD; Terry Kim, MD; David E. Rudnick, MA; Henry F. Edelhauser, PhD

Objectives: To characterize the uptake, washout, and metabolism of lidocaine hydrochloride in the iris/ciliary body and cornea.

Methods: Iris/ciliary body uptake of lidocaine hydrochloride was measured by incubating human and rabbit irides in radiolabeled carbon 14–1% lidocaine hydrochloride for 2 to 60 minutes. Washout was determined by incubating the iris in 14C–1% lidocaine hydrochloride for 5 minutes and transferring the iris to a series of wells. The wells contained a common intraocular irrigating solution of essential ions, glucose, and glutathione buffered with bicarbonate (an enriched balanced salt solution [BSS PLUS]), which is similar to aqueous humor. Corneal uptake was measured by exposing the endothelial surface to 14C–1% lidocaine hydrochloride for 5 or 15 minutes. Corneal washout was performed after 5-minute exposure to 14C–1% lidocaine hydrochloride using a 2-chambered diffusion apparatus. Samples of the iris, cornea, and BSS PLUS washout solution were analyzed by high-performance liquid chromatography and liquid scintillation spectrometry.

Results: In vitro iris/ciliary body uptake of 14C–1% lidocaine hydrochloride follows a logarithmic curve, with 50% to 60% of maximum lidocaine hydrochloride uptake present at 5 minutes. There was no difference in uptake between human, albino rabbit, and pigmented rabbit irides. Washout of lidocaine from the iris occurs with a half-life of 8 to 9 minutes. Corneal uptake of lidocaine was greater after incubation for 15 vs 5 minutes. The washout of lidocaine from the cornea had a half-life of 5 minutes. Results of high-performance liquid chromatography confirmed that there were no metabolites or breakdown products in the iris, cornea, or washout solution.

Conclusions: Lidocaine is taken up quickly by the iris/ciliary body and cornea and rapidly removed from these tissues after BSS PLUS washout. Irrigation during phacoemulsification seems to limit lidocaine exposure to the ocular tissues, resulting in a short duration of anesthesia. Lidocaine is not metabolized or broken down by the iris or cornea during this short period.


SUBCONJUNCTIVAL, topical, and intracameral anesthesia have been popularized recently as new techniques for use in cataract surgery. These anesthetic routes have potential safety advantages over traditional techniques such as retrobulbar and peribulbar anesthesia. Peribulbar and retrobulbar anesthesia can be complicated by globe perforation, retrobulbar hemorrhage, retinal vascular occlusion, extraocular muscle injury, optic nerve damage, brainstem anesthesia, and cardiac and respiratory arrest. In contrast, use of topical anesthesia has minimal risks. The benefits of topical administration of anesthesia include immediate onset of action, short duration, and early return of visual acuity with no postoperative diplopia, ptosis, or ecchymosis. However, there are shortcomings to topical administration of anesthesia, including inadequate blockade of sensory and motor nerves in the iris/ciliary body from incomplete absorption or dilution by tears. Therefore, patients may experience intolerance to the operating light microscope and discomfort from iris and lens manipulation during cataract surgery.

In the past, surgeons had to supplement topical anesthesia with peribulbar and subconjunctival or subtenon injections. Recently, intracameral administration of lidocaine has been introduced as an easy and expedient method of providing additional anesthetic effect. In this technique, 0.2 to 0.5 mL of unpreserved (methylparaben-free) 1% lidocaine hydrochloride is injected into the anterior chamber immediately after the paracentesis incision before viscoelastic injection and phacoemulsification. Intraocular administration of lidocaine anesthetizes the iris and ciliary body and greatly reduces patient discomfort during phacoemulsification and intraocular lens insertion.

Since the recent emergence of intracameral administration of lidocaine, inadequate information exists regarding its pharmacokinetics and distribution...
SUBJECTS, MATERIALS, AND METHODS

Radiolabeled carbon 14–1% lidocaine hydrochloride was obtained commercially (New England Nuclear, Boston, Mass). The specific activity was 10 μCi/μmol. An incubation media of 14C–1% lidocaine hydrochloride was made by mixing 14C–1% lidocaine hydrochloride, 50 μL, with unlabeled lidocaine hydrochloride powder, 20 mg (Sigma Chemical Co, St Louis, Mo), and an enriched balanced salt solution, 2.05 mL (BSS PLUS; Alcon Laboratories, Fort Worth, Tex), for a final concentration of 1% lidocaine hydrochloride. Results of high-performance liquid chromatography (HPLC) concluded that more than 99% of the radioactive label was associated with lidocaine hydrochloride. Etidocaine (Astra Pharmaceuticals, Westborough, Mass) was used as an internal standard for HPLC analysis.

New Zealand white (NZW) rabbits and Dutch Belted pigmented (DBP) rabbits weighing 2 to 3 kg were anesthetized with an intramuscular mixture of ketamine hydrochloride, 0.5 mL (30 mg/kg of body weight), and xylazine hydrochloride, 0.5 mL (4 mg/kg of body weight). The rabbits were euthanized with intracardiac injection of pentobarbital sodium, 324 mg/mL (1.0-mL Euthanasia-5 solution) (Henry Schein, Inc, Port Washington, NY), and the eyes were enucleated with the conjunctiva and eyelids intact. All experiments were conducted under the Association for Research in Vision and Ophthalmology guidelines for animal research.

Seven paired human eyes all with medium brown irides were received from the Georgia Eye Bank, Atlanta. The criteria for inclusion of the human eyes include a mean ± SEM donor age of 64.3 ± 7.9 years, a mean ± SEM death to enucleation time of 3.5 ± 1.0 hours, and a mean ± SEM donor age of 64.3 ± 7.9 years and enucleation to experiment time of 44.3 ± 8.4 hours. The eyes were stored in moist chambers at 4°C before experimentation.

IRIS/CILIARY BODY INCUBATION

The iris/ciliary body tissue was dissected and placed in a common intraocular irrigating solution containing essential ions, glucose, and glutathione buffered with bicarbonate (BSS PLUS), which is similar to aqueous humor, for a maximum of 4 hours. It has been shown20 that there is little change in the biochemical and physiologic responses of the iris when retained for up to 60 hours at 4°C. The iris/ciliary body tissue was cut into 4 similar segments with an approximate weight of 15 mg per segment and placed into the 14C–1% lidocaine hydrochloride incubation media. Each segment was incubated for 2, 5, 13, 30, or 60 minutes at 37°C. After incubation, the tissue was rinsed in BSS PLUS, blotted on filter paper, and weighed before placement in a scintillation vial. Solvable digest, 1.0 mL (Packard Instrument Co, Meriden, Conn), was added to the vial, and the tissue was placed in a shaking water bath until completely digested. Scintillation fluid, 10 mL (Ultima Gold, Packard Instrument Co), was added to the digest in the scintillation vial and analyzed for radioactivity in a liquid scintillation spectrometer (model LS7000, Beckman Instruments, Irvine, Calif). The rate of iris uptake of 14C–1% lidocaine hydrochloride was calculated by plotting total disintegrations per minute per milligram of iris vs time. These data were also converted to total micrograms of lidocaine hydrochloride per milligrams of iris by correcting for the unlabeled lidocaine hydrochloride added to the 1% incubation media. Statistical significance was determined by analysis of variance of the 3 uptake curve slopes.

CORNEAL INCUBATION

The paired rabbit corneas were excised and mounted on an 11.5-mm corneal ring in an in vitro dual-chambered specula microscope and perfused with BSS PLUS for a 1-hour stabilization period. The 14C–1% lidocaine hydrochloride incubation media, 100 μL, was applied to the endothelial surface of the paired corneas, and the corneas were incubated at 37°C for 5 and 15 minutes. After incubation, the lidocaine was removed from the endothelial surface using a surgical sponge. The corneas were rinsed 3 times by applying BSS PLUS to the posterior corneal surface and removing it with a surgical sponge. A corneal button was obtained using an 8.0-mm trephine. The button was separated through the stroma into its anterior and posterior segments using a dissecting microscope and fine-tipped forceps. Each half was weighed and digested and the radioisotope was counted as previously described. Paired t tests were used for statistical analysis. All values are expressed as mean ± SEM.

IRIS/CILIARY BODY WASHOUT

In a separate set of experiments, the iris/ciliary body tissue of humans and NZW and DBP rabbits were carefully dissected and placed in BSS PLUS. The iris/ciliary body tissue was cut into 2 approximately equal pieces and incubated in 14C–1% lidocaine hydrochloride for 5 minutes at 37°C. Each piece was removed, rinsed in BSS PLUS, and placed in a 24-well tissue culture plate containing BSS PLUS, 500 μL, in each well. The iris halves were incubated at 37°C in the first well for 5 minutes, in the second well for 10 minutes, and at intervals of 15 minutes thereafter. Aliquots of 250 μL of the BSS PLUS reservoir were removed and mixed with universal liquid scintillation cocktail for aqueous samples (Aquasol, Packard Instrument Co) before scintillation counting. After 15 minutes, the iris tissue was blotted on filter paper, weighed, and digested, and the tissue was added to the scintillation spectrometer. The counts were multiplied by uptake, distribution, and washout of lidocaine hydrochloride in the iris/ciliary body and cornea to determine its potential effectiveness and safety for intraocular use. In addition, we intend to determine if lidocaine is metabolized or broken down by the iris/ciliary body and cornea during a standard exposure time to these ocular tissues.
2 to obtain the radioactivity in the original 500-µL sample. The radioactivity of all periods was added with the radioactivity from the iris tissue digest. This number was the radioactivity present at point 0, before washout. The iris/ciliary body radioactivity, expressed in disintegrations per minute per milligram of tissue at each point, was plotted vs time. The total lidocaine uptake was expressed as micrograms of lidocaine hydrochloride per milligram of tissue. The iris/ciliary body half-life of 14C–1% lidocaine hydrochloride was determined from the logarithmic equation of the washout curve (disintegrations per minute per milligram of tissue vs time).

CORNEAL WASHOUT

Paired rabbit corneas were mounted on an 11.5-mm corneal ring, and the endothelial surface was exposed for 5 minutes to 14C–1% lidocaine hydrochloride incubation media. They were rinsed 3 times with BSS PLUS. Modified Ussing chambers were filled with BSS PLUS, 3.0 mL, on the endothelial and epithelial surfaces of the cornea. The BSS PLUS reservoirs bathing the endothelial and epithelial surfaces of the cornea were removed at 5 and 15 minutes and every 15 minutes thereafter for 90 minutes. The chambers were refilled with BSS PLUS after removal of the previous BSS PLUS solution. Samples of 1.5 mL of the original 3.0-mL BSS PLUS solution (epithelial and endothelial sides) were added to 10 mL of the universal liquid scintillation cocktail for aqueous samples and radioactively counted by scintillation spectrometry. All radioactive counts were multiplied by 2 to obtain the radioactivity in the original 3.0-mL sample. The cornea was trephined to 8.0 mm and digested, and the radioactivity was counted. The radioactive counts of all periods were added with the counts from the corneal digest. This number was the 0 point of incubation, before washout. The corneal radioactivity, expressed in disintegrations per minute per milligram of cornea at each point, was plotted vs time. Total lidocaine hydrochloride removal, expressed in micrograms of lidocaine hydrochloride per milligram of cornea, was plotted on a secondary axis. The corneal half-life of 14C–lidocaine hydrochloride removal, expressed in micrograms of lidocaine hydrochloride per milligram of cornea, was plotted on a secondary axis. The corneal half-life of 14C–lidocaine hydrochloride removal, expressed in micrograms of lidocaine hydrochloride per milligram of cornea, was plotted on a secondary axis. The corneal half-life of 14C–lidocaine hydrochloride removal, expressed in micrograms of lidocaine hydrochloride per milligram of cornea, was plotted on a secondary axis.

PREPARATION OF SAMPLES FOR HPLC ANALYSIS

Cornea and iris/ciliary body tissue in NZW and DBP rabbits was obtained after incubation in 14C–1% lidocaine hydrochloride. BSS PLUS washouts of the iris/ciliary body and cornea for NZW and DBP rabbits were also obtained for HPLC analysis. Extraction of lidocaine from the iris and cornea was carried out in 1.0-mL V-vials having caps with fluorocarbon resin liners. All solvents were redistilled in glass, and transfers during extraction (except transfers out of the mortar in which tissue samples were pulverized) were done using syringes that had fluorocarbon resin plunger seals with a flat face (SPECTRUM, Houston, Tex, or VICI Precision Sampling Corp, Baton Rouge, La). The 10-µL etidocaine internal standard was added to 1.0-mL cryovials, in which the samples were stored at -80°C before extraction. Samples consisted either of liquid volumes (300-300 µL) that were extracted without previous treatment or frozen samples of iris or cornea (8-24 mg) that were transferred into a stainless steel mortar with pestle for pulverization at liquid nitrogen temperature. The mortar was a cylinder (2.5 cm outside diameter × 7.0 cm long) snugly fitted with a fluorocarbon resin joint sleeve extending two thirds of its length beyond the top of the cylinder that contained an axial well (1.8 × 6.5 cm). An additional fluorocarbon resin joint sleeve was forced up to the top portion of the loose-fitting pestle with its flared end to retard movement of powdered tissue upward between the mortar and pestle. Samples (liquid or pulverized), with etidocaine internal standard present, were transferred by pipette to an initial 1.0-mL V-vial using a mixture of isopropyl alcohol, 100 µL, and n-propyl-amine, 100 µL. All transfers from the mortar to the V-vial were accomplished using a pipette tip with 4-mm cut from the end. The cryo sample vials and (if iris or cornea) the mortar and pestle were then rinsed with dichloromethane:isopropyl alcohol (3:1), 400 µL, and a second wash of dichloromethane:isopropyl alcohol, 200 µL, was also collected into the initial V-vial with an additional wash with dichloromethane:isopropyl alcohol, 200 µL. The first V-vial with transferred sample and washes was vortexed and centrifuged, and the lower phase was transferred to a second V-vial. The remaining aqueous phase in the first V-vial was then washed with hexane, 100 µL, and, after vortexing and centrifuging, the upper phase (hexane phase) of the first V-vial was combined with the first extraction in the second V-vial. The remaining aqueous phase and tissue residue in the second V-vial was vortexed and centrifuged so that the lower phase could be transferred to a clean V-vial in which it was dried down under a stream of helium. The inside of this final V-vial was then rinsed to the bottom with alcohol (20 µL) followed by n-propyl-amine (20 µL), centrifuged, and dried again. Each sample was then taken up in alcohol, 10 µL, and either stored for later analysis or appropriate aliquots injected immediately for measurement of radioactivity and optical density by HPLC analysis. High-performance liquid chromatography was carried out using a chromatography system (Millennium 2010, Waters, Milford, Mass) in conjunction with a radioactive flow counter (Radiometric A-140, Packard Instrument Co). The chromatography system uses a YMC-18 ODS-AQ reverse-phase minibore column (MCQ-112, 2.0 × 230 mm). Lidocaine emerges at 10.74 ± 0.87 minutes as a sharp optical density peak (205 nm) when eluted at 0.24 mL/min with a gradient of acetonitrile and water that increases from 15% to 80% acetonitrile.

RESULTS

IN VITRO IRIS/CILIARY BODY UPTAKE

Incubation of human brown (n = 8), NZW rabbit (n = 10), and DBP rabbit (n = 8) irides in the 14C–1% lidocaine hydrochloride incubation media showed that the iris/ciliary body uptake of 14C–1% lidocaine hydrochloride followed a logarithmic curve that seemed to plateau at 30 minutes in all irides (Figure 1). The maximum lidocaine hydrochloride uptake per milligram of iris tissue occurred at 60 minutes, with values of 75.87 ± 4.65, 67.90 ± 4.76, and 61.35 ± 10.23 µg of lidocaine hydrochloride per milligram of iris in
humans, NZW rabbits, and DBP rabbits, respectively. By 2 minutes, the tissue uptake of lidocaine was 32.41 ± 4.38, 30.72 ± 3.07, and 28.62 ± 1.38 µg of lidocaine hydrochloride per milligram of iris, respectively. This represented 43%, 45%, and 41%, respectively, of its maximum value (at 60 minutes) in all groups. By 5 minutes, this increased to 61%, 50%, and 59%, respectively. There was no difference in the rate of iris uptake of lidocaine hydrochloride among humans, NZW rabbits, and DBP rabbits (P = .63).

IN VITRO IRIS/CILIARY BODY EFFLUX

Iris/ciliary body lidocaine hydrochloride diffuses rapidly from the tissue after a sequential wash in BSS PLUS. Removal of lidocaine hydrochloride from the iris/ciliary body tissue follows a logarithmic decline in humans, NZW rabbits, and DBP rabbits (Figure 2). The efflux of the isotope had a half-life of 8.98, 8.45, and 8.70 minutes in the human, NZW rabbit, and DBP rabbit irides, respectively.

IN VITRO CORNEAL UPTAKE

Paired rabbit corneas (n = 10) showed an increased uptake of lidocaine at the 15- vs 5-minute incubation time (Figure 3). At 5 minutes, 14C–lidocaine hydrochloride uptake was 14.51 ± 1.39 µg of lidocaine hydrochloride per milligram of cornea in the anterior cornea and 13.30 ± 1.18 µg of lidocaine hydrochloride per milligram of cornea in the posterior cornea (P = .49). At 15 minutes, 14C–1% lidocaine hydrochloride uptake was 27.50 ± 1.96 µg of lidocaine hydrochloride per milligram of cornea in the anterior cornea and 23.08 ± 1.58 µg of lidocaine hydrochloride per milligram of cornea in the posterior cornea (P = .08). Total corneal uptake was 27.82 ± 2.51 and 50.58 ± 3.46 µg of lidocaine hydrochloride per milligram of cornea at 5 and 15 minutes, which was a significant difference between these 2 times (P<.001). Results of these studies also demonstrate that lidocaine hydrochloride can diffuse throughout the whole cornea even after exposure to only the endothelial surface.

IN VITRO CORNEAL EFFLUX

The lidocaine hydrochloride that was taken up by the cornea was able to diffuse from the tissue through the epithelial and endothelial surface. The epithelium did not seem to be a significant barrier to the efflux of lidocaine. Corneal removal of lidocaine hydrochloride follows a similar logarithmic decline (Figure 4) as the iris/ciliary body with a half-life of 5 minutes (n = 5).

HPLC ANALYSIS

Results of HPLC analysis of the iris/ciliary body, cornea, and BSS PLUS washout showed that lidocaine hydrochloride taken up and removed by the tissue was more than 99% lidocaine hydrochloride. The lidocaine hydrochloride was not metabolized, and no breakdown prod-

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ucts were detected. Figure 5 is a representative chromatogram of lidocaine hydrochloride extracted from a pigmented iris. Note that the $^{14}$C–1% lidocaine hydrochloride comes off the column at the same time as the optical density peak. Thus, results of the HPLC analysis show that it is indeed lidocaine hydrochloride that is taken up by the iris/ciliary body. Table 1 shows that more than 99% of the $^{14}$C–1% lidocaine hydrochloride was in the optical density peak for the iris/ciliary body and cornea. The BSS PLUS washout solution showed that more than 99% of the $^{14}$C–1% lidocaine hydrochloride was in the optical density peak for the iris/ciliary body and cornea. These data confirm that there is no metabolism or breakdown products of lidocaine hydrochloride by the ocular tissues.

Figure 3. Uptake of lidocaine hydrochloride in rabbit corneas after 5- and 15-minute incubations in radiolabeled carbon 14–1% lidocaine hydrochloride. Mean ± SEM anterior, posterior, and total corneal lidocaine hydrochloride uptake is expressed (n = 10). The left axis represents radiolabeled $^{14}$C–1% lidocaine hydrochloride; right axis, total lidocaine uptake.

Figure 4. Mean ± SEM washout of lidocaine hydrochloride from rabbit corneas after 5-minute incubation in radiolabeled carbon 14–1% lidocaine hydrochloride. The half-life is 5 minutes. The left axis represents $^{14}$C–1% lidocaine hydrochloride; right axis, total lidocaine uptake. Note that the slopes of the endothelial and epithelial side are nearly superimposed on each other.

Figure 5. High-performance liquid chromatograms of lidocaine hydrochloride extracted from a pigmented rabbit iris after 15-minute incubation in radiolabeled carbon 14–1% lidocaine hydrochloride. Radioactive counts are superimposed on optical density measurements. A, Chromatogram reduced 20 times to show the total optical density peak of lidocaine hydrochloride, the radioactive peak of lidocaine hydrochloride, and the internal standard etidocaine. B, Original chromatogram to further confirm that there is minimal metabolism of lidocaine.

Intracameral anesthesia is a promising new technique for ocular lidocaine administration. When local anesthetics such as lidocaine are placed near the nerve tissue, they penetrate the nerve sheath and block initiation and propagation of nerve impulses by decreasing the neuronal membrane permeability to sodium ions. This stabilizes the membrane, inhibits depolarization, and prevents the propagation of the action potential. Lidocaine is an amide anesthetic that is metabolized by the liver.\textsuperscript{28,29} The physicochemical properties that affect local anesthetics are lipid solubility, protein binding, and pKa dissociation constant.\textsuperscript{30,31} Drug potency is determined largely by its lipid solubility, and lidocaine has intermediate lipid solubility. The duration of anesthetic activity is related to the degree of protein binding of which lidocaine is in the intermediate group compared with other local anesthetics. The speed of onset is determined primarily by the pKa, which is the pH at which the ionized and nonionized forms exist in equal quantities. It is the uncharged form of the anesthetic that is responsible for the diffusion across the nerve sheath and membrane. Therefore, the onset of action is related to the amount of the drug that exists in its nonionized form. Lidocaine has a pKa of approximately 7.7. When injected into a tissue at a pH of 7.4, approximately 65% exists in the ionized form and 35% in the nonionized form. This relatively large amount of nonionized drug results in a rapid onset of action. Thus, lidocaine is a local anesthetic with intermediate potency, intermediate duration, and a rapid onset of action.\textsuperscript{28} These characteristics are desirable in cataract surgery regardless of whether it is administered through a topical, subconjunctival, or intracameral approach.

The innervation of the iris is dense and formed by the sensory and autonomic fibers of the long and short posterior ciliary nerves. A plexus of efferent fibers exist along the muscle fibers of the iris, and additional unmyelinated fibers penetrate the iris stroma. In unmyelin-
sification. Gills et al23 report lower pain scores during
viscoelastic injection, capsulorrhexis, and phacoemul-
ter the paracentesis incision is made.23 This is followed
served lidocaine hydrochloride without epinephrine af-
myelinated small nerve fibers in the iris stroma.
the iris and is most likely directly absorbed by the un-
cameral injection, lidocaine is able to readily diffuse into

The intracameral approach to lidocaine injection in
cataract surgery is to inject 0.2 to 0.5 mL of 1% unpres-
served lidocaine hydrochloride without epinephrine af-
er the paracentesis incision is made.23 This is followed by viscoelastic injection, capsulorrhexis, and phacoemul-
sification. Gills et al23 report lower pain scores during phacoemulsification and intraocular lens insertion in pa-
ients receiving 0.1 and 0.5 mL of intracameral lido-
caine hydrochloride vs those receiving balanced salt so-
. In addition, there were no differences in preoperative or postoperative endothelial cell counts.23

The injection of 1% unpreserved lidocaine hydro-
chloride, a drug not formulated for intraocular use, raises the issue of safety and drug distribution. It is well known that preservatives, pH, concentration, and osmolality can cause corneal endothelial effects.23-33 Gonnering et al34 demonstrated that structural alterations lead to a breakdown in the barrier function of the corneal endo-
thelium outside the pH range of 6.5 to 8.5. The pH of 1% unpreserved lidocaine hydrochloride was previously mea-
sured by Kim et al36 to be 6.4, which was lower than that of BSS PLUS (pH of 7.4). However, the package insert of lidocaine hydrochloride lists a pH of 6.0, with a range of 5.0 to 7.0. Lidocaine has a weak buffering capacity (Table 2) and readily achieves a neutral pH with a small volume of BSS PLUS. Therefore, it can be assumed that lidocaine, 0.2 mL, injected intracameraly is buffered im-
mediately by approximately 21 µL of aqueous humor to a physiologic pH of 7.0. The osmolality of 1% lidocaine
hydrochloride measured by Kim et al36 was 302 mOsm/kg, similar to BSS PLUS, which had an osmolality of 305 mOsm/kg.

Drug concentrations can have various effects on ocu-
tular tissues. In a recent study,37 0.2 mL of bupivacaine hy-
drochloride (0.75%), unpreserved lidocaine hydrochlor-
ide (4%), and proparacaine hydrochloride (0.5%) was
jected into the anterior chamber of rabbits. Twenty-
four hours later, an increase in corneal thickness and cor-
neal opacificication was apparent. However, these concen-
trations were much higher than those presently being used for intracameral anesthesia during routine phacoemul-
sification. Furthermore, when diluted 1:10, there was no significant increase in corneal thickness or opacifica-
ion after injection of the same anesthetics.37

Perhaps the most important consideration in the
safety of intracameral anesthetics is whether a preserva-
tive is present. It is well known that preservatives used in ocular medications can be toxic to the endo-
thelium.38-40 Sodium bisulfite has previously been shown to be toxic to the corneal endothelium when adminis-
ted by intracameral injection43 or by perfusion in rabbit cor-
neas.40 Methylparaben (methyl p-hydroxybenzoate) is the most commonly used preservative in local anesthetics and has been shown39 to cause corneal endothelial effects in rabbits. Most single-use vials will be labeled lidocaine methylparaben free. Multiple-use vials should never be used intraocularly. It is important for surgeons using intraocular anesthetics to be alert to potential problems caused by preservatives, pH, and concentration.

Despite these concerns, use of 1% unpreserved lidocaine hydrochloride seems to be reasonably safe to the cor-
neal endothelium. Kim et al40 evaluated the effect of ad-
ministration of 1% unpreserved lidocaine hydrochloride on corneal endothelial cell function, ultrastructure, and vi-
ability. Rabbit and human corneas were directly perfused with 1% lidocaine hydrochloride methylparaben free for 15 minutes, followed by a 2- to 3-hour washout with BSS PLUS. The corneas perfused with lidocaine caused endo-
thelial cell edema, which reversed on removal of lidocaine from the perfusion media. Furthermore, the corneal swelling and deswelling rates were not significantly different between the lidocaine and control groups. Results of electron microscopy of the rabbit corneas showed only transient cell edema and healthy ultrastructure. In human eye bank corneas (moist chamber), endothelial cell viability was simi-
larly unchanged after exposure to lidocaine. Further studies are needed to evaluate the effect on the retina and other ocular tissues.

The second concern of using 1% unpreserved lido-
caine as an ocular anesthetic is the lack of scientific in-

Table 1. High-Performance Liquid Chromatography Analysis Showing the Amount of Radiolabeled Carbon 14–1% Lidocaine Hydrochloride Present in the Optical Density Peak vs the Total Injected*  

<table>
<thead>
<tr>
<th></th>
<th>Total 14C, dpm</th>
<th>Lidocaine Peak, dpm</th>
<th>Lidocaine Recovery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iris and ciliary body (n = 14)</td>
<td>5102.5 ± 173.2</td>
<td>5085.3 ± 171.0</td>
<td>99.67 ± 0.07</td>
</tr>
<tr>
<td>Cornea (n = 4)</td>
<td>3636.8 ± 1187.3</td>
<td>3631.0 ± 1185.8</td>
<td>99.64 ± 0.50</td>
</tr>
<tr>
<td>Iris and ciliary body wash (n = 9)</td>
<td>3083.1 ± 612.6</td>
<td>3072.0 ± 611.3</td>
<td>99.63 ± 0.11</td>
</tr>
<tr>
<td>Corneal wash (n = 13)</td>
<td>337.2 ± 121.6</td>
<td>331.2 ± 122.3</td>
<td>91.69 ± 5.59</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SEM.

Table 2. Amount of Enriched Balanced Salt Solution (BSS PLUS) to Buffer 1% Lidocaine Hydrochloride (n = 3)*  

<table>
<thead>
<tr>
<th>pH</th>
<th>BSS PLUS Added to 200 µL of 1% Lidocaine Hydrochloride, µL ± SEM</th>
<th>BSS PLUS Added to 500 µL of 1% Lidocaine Hydrochloride, µL ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.00</td>
<td>21 ± 0.0010</td>
<td>52.5 ± 0.0030</td>
</tr>
<tr>
<td>7.20</td>
<td>58 ± 0.0009</td>
<td>145.0 ± 0.0020</td>
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<tr>
<td>7.34</td>
<td>157 ± 0.0007</td>
<td>392.5 ± 0.0017</td>
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* Initial pH of 1% lidocaine hydrochloride (Astra Pharmaceutical, Westborough, Mass) = 6.67 ± 0.04 (n = 3). Initial pH of BSS PLUS = 7.34 ± 0.02 (n = 3).
formation regarding distribution and pharmacokinetics in ocular tissues. During intracameral injection, lidocaine hydrochloride is exposed directly to the iris/ciliary body and corneal endothelium. We determined that iris and corneal uptake and release of lidocaine occurs within 5 to 10 minutes. Therefore, an in vitro design was used in this study to enable precise quantitation of lidocaine uptake and release in a short period. Furthermore, the in vitro study is similar to what would occur after anterior chamber injection of lidocaine, 0.2 mL. The anterior chamber acts as a depot, allowing the lidocaine to diffuse directly into the cornea and iris. Once phacoemulsification is started, there would be reverse diffusion of lidocaine from the cornea and iris to the intraocular irrigating solution similar to the stepwise washout procedure used in the in vitro study.

Our results show that iris uptake follows a logarithmic curve that seems to stabilize by 30 minutes. At 5 minutes, the time when many surgeons are performing phacoemulsification and intraocular lens insertion, lidocaine hydrochloride is at 50% to 61% of its maximum 60-minute concentration in the iris/ciliary body. There is no statistically significant difference between the uptake of albino and pigmented irides, suggesting that the amount of binding of the drug to melanin is insignificant. Therefore, it may be unnecessary to adjust dosage or concentration in patients with pigmented irides.

Removal of lidocaine hydrochloride from the cornea after a 5-minute exposure to 1% lidocaine hydrochloride follows a logarithmic curve of decline. The 5-minute incubation time was chosen because it simulates the amount of time the lidocaine hydrochloride would be exposed to the iris/ciliary body during routine, uncomplicated phacoemulsification. On washout, which is similar to irrigation during phacoemulsification (in which approximately 150-250 mL of an irrigation solution is infused through the anterior chamber), half of the drug concentration would be removed from the extracellular space surrounding the nerves of the iris/ciliary body in 8 to 9 minutes. This is similar to the 10-minute effect of anesthesia observed after intracameral injection of 1% unpreserved lidocaine hydrochloride during cataract surgery. Complicated procedures may require additional anesthesia.

Increasing the exposure time of lidocaine hydrochloride to the cornea increases the corneal uptake of lidocaine hydrochloride, with no significant difference between uptake in the anterior vs posterior cornea. Similarly, the continuous irrigation during phacoemulsification is extremely important in lowering the corneal lidocaine concentration, thus limiting potential endothelial damage. In fact, when the cornea receives continuous washout after a 5-minute incubation in 1% lidocaine hydrochloride, the half-life of the drug in rabbit corneas is 5 minutes. Such a short exposure time may indicate why only transient corneal endothelial cell edema without ultrastructural changes in the endothelium occurs after in vitro perfusion of 1% lidocaine hydrochloride. Irrigation during phacoemulsification is probably the reason there are limited clinical reports of adverse effects on the cornea from the use of intracameral lidocaine hydrochloride.

It is well known that lidocaine hydrochloride is metabolized in the liver to 2 active metabolites, monoethylglycineexilidide and glycineexilidide. However, results of HPLC analysis confirm that a short exposure of lidocaine hydrochloride to the iris/ciliary body and cornea results in no metabolites. Metabolites contain different physicochemical properties and can often be more toxic or display different pharmacokinetics than the parent compound itself.

In summary, 1% lidocaine hydrochloride injected intracameral during ocular surgery seems to be rapidly taken up by the iris/ciliary body and cornea. The half-life of lidocaine in the iris/ciliary body and cornea is short and consistent with the time it has been reported to be efficacious clinically. The lack of clinical toxic effects is because of the short time lidocaine is exposed to the ocular tissues because of the copious irrigation used during phacoemulsification. There is no metabolism of lidocaine in the cornea or the iris/ciliary body. If intracameral lidocaine is used as a routine anesthetic in phacoemulsification, a formulation more compatible with intraocular tissues should be considered.

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REFERENCES

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Book Review
Ophthalmology During the War and in the Future

The distinguished ophthalmologists briefly reviewed the developments in ophthalmology during the war years and offered predictions as to the direction of future investigations. In ophthalmic surgery, technics of dealing with intraocular foreign bodies were revolutionized, and the ingenious Berman locator was devised. Concepts of the minute central localization of the visual functions were put on a secure observational basis. Novel and fruitful suggestions in the fitting of artificial eyes were made. In ophthalmic medicine, the greatest advance was made in chemotherapy. Knowledge of the optics of gunsights, range finders, periscopes, graticules, and viewing and scanning devices; uses of goggles; problems of dazzle, scatter and haze, and above all, of night vision and dark adaptation have increased beyond all bounds.