REVIEW ARTICLE

Topical Anesthetics for Dermatologic Procedures: A Review

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BACKGROUND Practitioners are increasingly using topical anesthetics to decrease the pain associated with superficial dermatologic, aesthetic, and laser procedures. Numerous lidocaine-containing products are available, but comprehensive reviews are lacking regarding their relative safety profiles and appropriate dermatologic uses.

MATERIALS AND METHODS A literature review of currently available topical anesthetics, their safety profiles, and dermatologic uses was conducted.

RESULTS Factors that should be considered to reduce the risk of side effects associated with the use of topical anesthetics include the amount of product used, body location, size of the surface area, and duration of product application. Many case reports document adverse outcomes associated with the use of compounded products that the Food and Drug Administration has not approved that have inappropriately high anesthetic concentrations and from the use of topical anesthetics on excessively large skin surface areas during laser treatments.

CONCLUSIONS Lidocaine-containing products play an integral role in cutaneous anesthesia by providing patient comfort with minimal side effects. Careful attention must be paid to the particular anatomic location, the total surface area covered, and the duration of anesthetic skin contact.

The authors have indicated no significant interest with commercial supporters.

Topical anesthetics decrease pain during cutaneous procedures in the outpatient setting and permit a variety of dermatologic procedures to be performed without anatomic distortion from local anesthetic injection. As the number of in-office dermatologic procedures continues to grow, practitioners will benefit from awareness of the indications, pharmacologic mechanisms, appropriate methods of application, and safety profiles of the currently available prescription and over-the-counter (OTC) topical anesthetics.

Historical Background of Topical Anesthetics

"Coca" was a term used by the Incas for the substance derived from the plant *Erythroxylum coca*. The Incas initially reserved the use of coca for their monarch during religious ceremonies. After discovering its anesthetic and stimulatory properties, Peruvians subsequently began to cultivate the plant for commercial distribution. Over time, the plant became a staple of Peruvian culture. Peruvians carried the plant in sidebags called "chuspas" to have it available for chewing.[1] In 1860, Niemann isolated the plant's active ingredient, cocaine,[2] but it was not until 1884 that ophthalmic surgeon Karl Koller demonstrated that general anesthesia could be avoided for ophthalmic procedures by application of cocaine to the conjunctiva.[3] Additional ester anesthetics, such as procaine and tetracaine, were created in the early 20th century, but these were noted to result in high rates of allergic contact dermatitis. In 1943, Loefgren synthesized the first amide anesthetic, lidocaine. Subsequently, a large number of topical formulations of esters, amides, and adrenalines have been developed and

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used for dermatologic procedures.[4] Although the topical formulations are generally safe, allergic reactions, systemic absorption, and death can occur when care is not observed with use of these products.[5–10]

Classification and Mechanism of Topical Anesthetics

Local anesthetics structurally consist of three parts: an aromatic ring, an intermediate chain, and an amine group (Figure 1). The aromatic ring is lipophilic and enables diffusion of the anesthetic through the highly lipophilic nerve membrane.[11] The lipophilicity of an anesthetic is directly proportional to its potency.[12] The intermediate chain, which connects the aromatic and amine portions, determines the classification of local anesthetics as an ester or amide. Ester and amide anesthetics differ in their chemical stability and metabolism. Esters are hydrolyzed by plasma cholinesterases and form para-aminobenzoic acid, a common allergen. Amides tend to be more stable and less allergenic and are metabolized in the liver by microsomal enzymes.[13,14] The protein-binding characteristics influence the duration of the anesthetic. Larger chemical groups added to the aromatic and amine portions increase the duration of activity.[15] Because amides are metabolized in the liver, use of amide anesthetics should be considered a relative contraindication in those with liver disease.[14] Regardless, amide anesthetics are often prescribed in patients with known and unknown liver disease without guidelines specifying appropriate dose modifications.

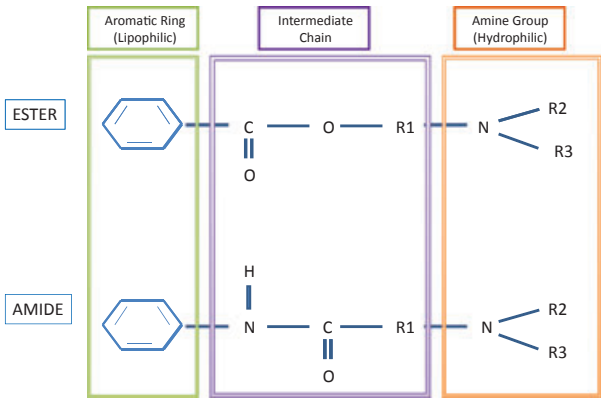

Figure 1. Basic structure of anesthetics.

To be effective, topical anesthetics must traverse the superficial layers of skin and affect the nerve endings within the dermis. The thickness of the stratum corneum and the acid dissociation constant (pK_a) of an anesthetic determine how well the topical medicine can penetrate the stratum corneum.[13] When the pK_a closely matches the pH of normal skin (~5.5),[16] and when the stratum corneum is thin, such as on the eyelid, the compound can pass through the outer layer of skin more readily.[14] Topical anesthetics are also able to penetrate mucosal surfaces, such as the mouth, genitals, and conjunctiva more easily than through a keratinized surface because of the absence of a stratum corneum.

Several techniques can improve dermal absorption of topical anesthetics. Removing the stratum corneum with preoperative procedures such as tape stripping, degreasing with acetone, or laser ablation enhances dermal absorption.[17,18] Occlusion and heat can also facilitate anesthetic penetration into the skin.[19] Iontophoresis enhances absorption of topical anesthesia by using an electric current to facilitate the passage of ionized local anesthetic into and across the skin barrier.[11] Adding epinephrine to local anesthetic induces vasoconstriction, which slows the anesthetic's removal and increases the duration of its local tissue effect.[20,21]

Once inside the dermis, ester and amide anesthetics possess the same mechanism of action (Figure 2). The anesthetic binds the voltage-gated sodium channel of the free nerve endings and blocks sodium influx. The blockade of sodium influx inhibits nerve cell depolarization and prevents propagation of nerve cell impulses along the nerve.[22] Nerve fibers are categorized into three major anatomic classes: myelinated somatic nerve fibers (A fibers), myelinated preganglionic autonomic fibers (B fibers), and

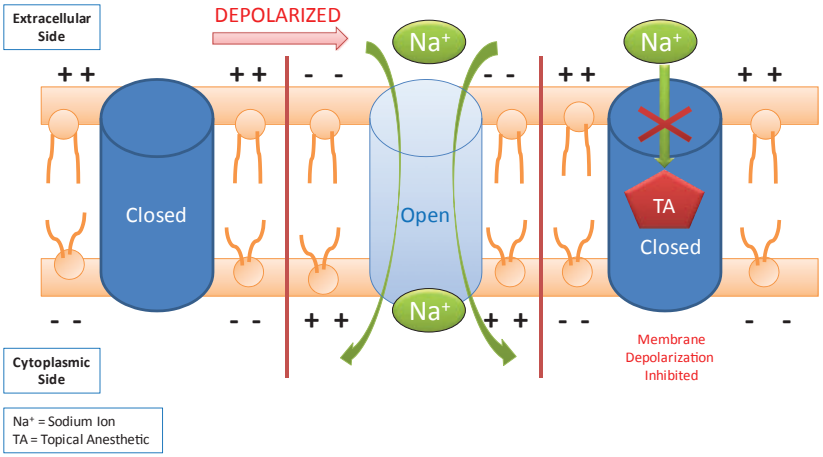

Figure 2. Nerve cell membrane depolarization and inhibition of depolarization by binding of topical anesthetic.

nonmyelinated axons (C fibers).[23] Topical anesthetics first impede conduction of myelinated autonomic B fibers, which regulate vascular smooth muscle tone, followed by blockade of nonmyelinated C fibers and, finally, myelinated A fibers, which regulate pain and temperature.[24] Topical anesthetics have proven efficacy, as demonstrated by multiple studies testing for anesthesia effect with various painful stimuli, including venipuncture,[25] pin-prick testing,[26] and split-thickness skin graft donation.[27] Many feel that laser-induced pain sensation is the optimal method of testing anesthetic efficacy because the stimuli are well controlled and easily reproducible and selectively activate polymodal nociceptors without disrupting mechanosensitive receptors.[28,29]

Application and Clinical Use

Fear of needles and pain can cause anxiety in patients awaiting procedures in the outpatient setting.[30,31] Application of topical anesthetic before or in place of injection of local anesthetic can help to relieve anxiety. Patients can apply the topical anesthetic before arriving at the office, assuming they have proper instructions on its safe application. Safe application entails gently washing the area to be treated with a mild cleanser and water to eliminate contaminants (e.g., makeup, dirt) that could hinder the absorption or efficacy of the anesthetic. Patients should avoid skin cleansing with benzoyl peroxide, which may decrease the topical anesthetic's absorption.[32] Patients may use a tongue depressor or gloved finger to apply a uniform layer of cream approximately 1/8″ thick. If the product is applied with a bare finger, the anesthetic should be immediately washed off the digit once adequate application to the desired area occurs. Depending upon the anesthetic used, the product is left in place for 30 to 60 minutes. Occlusion with plastic wrap or massaging the cream into the skin may achieve quicker onset of action, if necessary. Immediately preceding the procedure, the material is removed with dry gauze, and the skin is wiped clean with water-dampened gauze. Complete removal of residual cream before laser procedures is particularly important with alcohol-containing topical anesthetics because of their incendiary potential.[11]

It must be emphasized to the patient that improper product use can result in dire adverse events. The U.S. Food and Drug Administration (FDA) issued a public health advisory in 2007 reporting at least two instances of death when young women applied topical anesthesia under occlusion to their legs before laser hair removal.[33] The advisory recommended that patients use only FDA-approved topical anesthetics with the lowest concentration of anesthetic for the shortest amount of time necessary.

Because the risk of adverse events with improper application is real and could lead to subsequent medicolegal action, physicians must exercise caution and good judgment when educating patients on home use of topical anesthetics. If a large area of skin is involved, treatments should be divided into smaller anatomic portions so that appropriately sized segments of skin are anesthetized and treated during each session.

Most manufacturers make recommendations on safe product application based upon estimates of body surface area. the U.S. Office of Health and Environmental Assessment has summarized specific direct techniques to measure total body surface area precisely in detail.[34] These measurements include coating the body part with a substance of known area, triangulation of linear dimensions, and surface integration using a planimeter.[35] Unfortunately, for practitioners advising patients on safe topical anesthetic use, these modalities are cumbersome and impractical. Other methods of body surface area estimation include use of formulae that take into account body dimensions such as height and weight, but these calculations can also be burdensome. A simpler method of estimating body surface area may be use of reference tables developed by the U.S. Environmental Protection Agency that were created via regression equations and the National Health and Nutrition Examination Survey II height and weight data. Tables 1 and 2 are adaptations of these figures and allow the reader to gain an appreciation for the size (cm^2) of anatomic parts.

TABLE 1. Surface Area of Adult Men (cm^2)

	Percentile				
Body Part	*10th* cm^2	*25th*	*50th*	*75th*	*95th*
Total	17,200	18,200	19,400	20,700	22,800
Head	1,210	1,240	1,300	1,350	1,430
Trunk (includes neck)	6,220	6,740	7,390	8,070	9,350
Arms	2,520	2,700	2,910	3,140	3,540
Forearms	1,110	1,210	1,310	1,440	1,660
Hands	880	930	990	1,050	1,170
Thighs	3,310	3,540	3,820	4,110	4,630
Lower legs	2,260	2,400	2,560	2,720	2,990
Feet	1,180	1,,240	1,310	1,380	1,490

TABLE 2. Surface Area of Adult Women (cm^2)

	Percentile				
Body Part	*10th* cm^2	*25th*	*50th*	*75th*	*95th*
Total	14,900	15,800	16,900	18,200	20,900
Head	1,070	1,090	1,110	1,140	1,170
Trunk (includes neck)	5,070	5,380	5,790	6,360	7,520
Arm	2,140	2,210	2,300	2,380	2,530
Hands	746	770	817	868	966
Thighs	2,810	3,000	3,260	3,570	4,210
Lower legs	1,920	2,040	2,180	2,330	2,610
Feet	1,030	1,080	1,140	1,210	1,340

Specific FDA-Approved Topical Anesthetics

Topical anesthetics exist in many different preparations and vehicles for delivery. Eutectic mixtures allow individual anesthetic compounds, which are normally in the solid state at room temperature, to be combined as liquids. Eutectic mixtures permit higher concentrations of anesthetic to be used safely and facilitate application to the skin.[21] Liposomal encapsulation is another vehicle that facilitates percutaneous drug delivery. Liposomes are microscopic, spherical, phospholipid-based carriers that deliver a greater concentration of local anesthetic to sensory nerves than other conventional formulations with lower lipophilicity.[33,34,36,37]

Improper application of topical anesthetic preparations such as benzocaine, lidocaine, and tetracaine may cause serious complications, including death. Prolonged application, use of inappropriately high concentrations, and application to large surface areas before outpatient procedures increase the risk of cardiotoxicity and central nervous system

toxicity.[5–10,38] In general, the central nervous system is more susceptible to the pharmacologic actions of local anesthetics than is the cardiovascular system.[39] The initial symptoms of anesthetic-induced toxicity include lightheadedness, circumoral numbness, diplopia, and tinnitus. (See Table 3 for additional signs and symptoms of lidocaine toxicity.) Many adverse reactions also appear to be related to the inclusion of epinephrine within the anesthetic mixture.[5]

In 2006, the FDA warned five pharmacies to discontinue compounding standardized versions of topical anesthetic creams that were already available for general distribution.[40] Concern grew because of the presence of higher concentrations of the compounded anesthetic mixtures than in the FDA-approved products. In addition, the compounded products often lacked appropriate warnings or directions for use. Many of the compounded anesthetics that received a warning from the FDA included products with unknown strengths of active anesthetic and also contained sympathomimetic agents such as phenylephrine, which limits the compounded product's shelf life because of light sensitivity and increases adverse events related to hypertension and vasoconstriction.[41,42] Standardization of compounded products proves difficult because individual pharmacies use different protocols to mix various ingredients in their topical anesthetics.[11]

TABLE 3. Signs and Symptoms of Lidocaine Toxicity

Blood Lidocaine Levels, μg/mL	*Signs and Symptoms*
1–5	Tinnitus, lightheadedness, circumoral numbness, diplopia, metallic taste in the mouth
5–8	Nystagmus, slurred speech, localized muscle twitching, fine tremors
8–12	Focal seizure activity, which may progress to tonic-clonic seizures
20–25	Respiratory depression which can lead to coma

Despite this FDA warning, a large number of pharmaceutically compounded topical anesthetics remain in use for outpatient procedures such as laser hair removal or soft tissue augmentation (Table 4). Their mechanism of action is similar to that of FDA-approved products, but higher concentrations and various active anesthetics are mixed

TABLE 4. Pharmaceutically Compounded Topical Anesthetics

Non-FDA Approved Product	*Active Ingredients*
BLT	20% benzocaine, 6% lidocaine, 4% tetracaine
TAC	0.5% tetracaine, 1:2000 epinephrine, 11.8% cocaine
LET	4% lidocaine, 1:2000 epinephrine, 0.5% tetracaine
Topex, Topicale, HurriCaine, Comfortcaine, Gingicaine	Benzocaine 20%
Lasergel*	10% lidocaine, 10% tetracaine
Lasergel plus 10/10*	10% lidocaine, 10% tetracaine, 0.5% phenylephrine
Photocaine gel*	6%lidocaine, 6% tetracaine
Anesthetic skin lotion*	10% lidocaine, 2% prilocaine
Anesthetic skin gel 3+*	Lidocaine, prilocaine, tetracaine
Tetracaine 6% in DMSO in gel*	6% tetracaine in DMSO
Triple kwick anesthetic gel*	Benzocaine, lidocaine, tetracaine
Kwick anesthetic gel*	Benzocaine, lidocaine, tetracaine, DMSO
N-E-W topical anesthetic*	30% lidocaine, 2% prilocaine, 4% tetracaine
Lidocaine and tetracaine demi gel*	Lidocaine, tetracaine
ExtraStrength triple anesthetic cream*	20% benzocaine, 6% lidocaine, 4% tetracaine
Betacaine LA ointment*	15% lidocaine, 5% prilocaine, phenylephrine
Betacaine Plus ointment*	15% lidocaine, 5% prilocaine

*Received a warning from the U.S. Food and Drug Administration in 2005.

together. Significant variability in product quality and accurate dosing of these compounded products becomes difficult because they are packaged in widely different containers. Kravitz[41] noted that these compounded products have a low therapeutic index and are often improperly labeled. All of these factors increase the risk of adverse events, including overdose, seizures, arrhythmias, and death and should prompt practitioners to limit the use of topical anesthetics to those approved by the FDA. The remaining portions of this chapter will focus on topical anesthetics approved by the FDA for use during outpatient dermatologic procedures.

Eutectic Mixture of Local Anesthetics

The prescription topical lidocaine product most widely used is or eutectic mixture of local anesthetics (EMLA; Astra Pharmaceuticals, Westborough, MA). EMLA is an oil-in-water emulsion of 2.5% lidocaine and 2.5% prilocaine. As mentioned above, the eutectic mixture possesses a melting point lower than room temperature, allowing both anesthetics to exist as liquids rather than as crystals.[43] The polyoxyethylene fatty acid emulsifiers present within EMLA allow for enhanced absorption of the product.[44] As such, although the true concentration of anesthetic is 5%, leading to lower risk of systemic toxicity, the cream has greater potency because of the emulsified oil droplets.[14,45]

The duration of application, the size of the treated area, and the specific anatomic location treated determine the amount of lidocaine and prilocaine systemically absorbed from EMLA cream. Occlusion and longer duration of application increase its penetration and efficacy.[46–48] Body locations with thin or absent stratum corneum, such as the eyelid and mucosa, absorb anesthesia more readily than skin on the back or hands. Analgesia is achieved to a depth of 3 mm after 60 minutes of application, and a maximum dermal depth of 5 mm is reached after 120 minutes.[49,50] Dermal analgesia continues even after removal of the topical anesthesia, presumably because accumulation of the product in the stratum corneum.[28,51]

After application on the skin, EMLA produces a biphasic response with initial vasoconstriction and blanching that peaks after 90 minutes of application. After 2 to 3 hours of application, a rebound vasodilation occurs that results in skin erythema,[51] which should not be confused with other rare adverse cutaneous reactions such as contact urticaria or allergic contact dermatitis.[52,53] It appears that prilocaine is the agent that plays a role in allergenicity.[54]

Despite the low risk of system toxicity when 60 g EMLA cream is applied to 400 cm^2 of intact skin under occlusion for 24 hours (peak lidocaine levels <1/20 the systemic toxicity level, prilocaine <1/36 toxicity; AstraZeneca insert), practitioners must beware of potential side effects. Use on damaged or inflamed skin or on a large surface area (2,000 cm^2) may increase the risk of systemic side effects. The prilocaine portion of EMLA can induce methemoglobinemia because of its ability to oxidize iron in red blood cells from the ferrous to the ferric state, impairing hemoglobin transport of oxygen. When levels of methemoglobin are between 15% and 30%, patients present with initial signs of cyanosis.[15] Methemoglobin levels of 30% to 50% result in dyspnea, tachycardia, and headache. Methemoglobin levels greater than 50% are associated with lethargy and coma.[7] EMLA should not be used in patients with congenital or idiopathic methemoglobinemia or in infants younger than 12 months who are being treated with methemoglobinemia-inducing medications such as sulfonamides, phenazopyridine, dapsone, acetaminophen, nitrates, nitrites, and phenobarbital (AstraZeneca insert).

EMLA is a pregnancy category B agent, but caution should be exercised when being administered to a nursing mother, because lidocaine is excreted through breast milk (AstraZeneca insert). EMLA cream is safe to administer on intact skin of full-term neonates, but care must be taken to limit the dose and area of application (e.g., maximum dose of 1 g applied for 1 hour).[55] No differences in

EMLA safety have been noted for the geriatric population (Table 2). Because EMLA contains sodium hydroxide, its use must be avoided around the eyes to prevent alkaline chemical injury.[56,57]

Lidocaine Lidocaine, alone or in combination with another anesthetic, is the most widely used topical anesthetic. It belongs to the amide class of anesthetics, which has less risk of inducing an allergic reaction than ester anesthetics. Brand names for OTC topical lidocaine include Topicaine (ESBA Laboratories, Jupiter, FL), Lidoderm (Endo Pharmaceuticals, Chadds Ford, PA), and LMX (Ferndale Laboratories, Ferndale, MI). Topicaine is a 4% or 5% lidocaine gel, and Lidoderm is a 5% lidocaine adhesive patch. LMX is a 4% or 5% lidocaine liposomal delivery cream that has several lipid bilayers, which facilitate dermal penetration of anesthetic and protect the drug from being rapidly metabolized, allowing LMX to achieve the same analgesia as EMLA in a shorter period of time without requiring occlusion.[58]

Lidocaine is classified as pregnancy category B because animal studies have not shown risk to the fetus, but controlled human studies have not been conducted. As mentioned with EMLA, caution should be exercised when administering topical lidocaine to a nursing mother, because the milk: plasma ratio of lidocaine is 1:4 (LMX insert). Care must be exercised with use of topical lidocaine around the eye because accidental eye exposure will result in severe corneal irritation.

S-Caine Peel and S-Caine Patch An S-Caine peel, marketed as Pliaglis (Galderma Laboratories, Fort Worth, TX), was discontinued in September 2008. This product was a novel eutectic mixture of 7% lidocaine and 7% tetracaine in a cream base. After application to the skin, the cream dried and formed a flexible film that fixed the anesthetic into position until the film was peeled off the skin. It was believed that the flexible film served as an occlusive dressing that facilitated drug absorption or deposition into the skin.[59,60] Distribution of the S-Caine peel was eventually terminated because of an inability to obtain consistent product viscosity. Plans for its re-release are unclear. The S-Caine Patch (Zars, Inc, Salt Lake City, UT) contains a small amount of topical anesthetic under a patented heating element that raises the temperature to 40°C for longer than 14 hours and enhances delivery of the anesthetic. This product is marketed as Synera and contains a eutectic mixture of 70 mg of lidocaine and 70 mg of tetracaine. The heating system portion of the patch is activated through an exothermic reaction when oxygen interacts with the internal components of iron powder, activated carbon, wood flour, sodium chloride, and water. When the patch is applied to the skin, it increases the skin temperature approximately 5°C, but the maximum skin temperature produced by the patch at the site of application does not exceed 40°C.[61] The mean depth of analgesia has been measured to at least 6.8 mm.[62] The product manufacturer states that the patch should be placed on intact skin 30 minutes before superficial dermatologic procedures such as a shave biopsy. Erythema, blanching, and edema are the most commonly observed local reactions (product insert).

Clinical Applications of Topical Anesthetics

Topical anesthetics are a versatile supplement to the practice of outpatient dermatologic procedures. Application of topical anesthetics has proven to decrease pain associated with common procedures such as shave biopsies, punch biopsies, curettage, and electrosurgery.[63–66] Laser and aesthetic medicine have been strong drivers of the growth of outpatient dermatologic procedures in recent history. Listed below are popular uses of topical anesthetics for aesthetic procedures.

Laser and Light-Based Procedures

The most common laser procedure for which topical anesthetics are used is laser-assisted hair removal, particularly in such sensitive areas as the upper lip and inguinal region. One study demonstrated that

both of the most commonly used lidocaine preparations (EMLA and LMX-5) reduced discomfort associated with neodymium-doped yttrium aluminum garnet (YAG) laser hair removal, but there was no statistically significant difference in pain reduction between the two products after a 30-minute unoccluded application time.[67] Topical lidocaine has also been shown to reduce the intense hot needle-like sensations during Q-switched laser tattoo removal.[68]

Discomfort associated with laser treatment of vascular (e.g., port-wine stain, telangiectasia, hemangioma) and pigmented (e.g., lentigo, café-au-lait macule) lesions can be minimized with topical lidocaine-containing anesthetics.[69–71] Although the vasoconstrictive effect of the prilocaine contained in EMLA generally results in a blanching effect, 60-minute EMLA application has been demonstrated to be safe and effective in the pulsed dye laser treatment of ectatic blood vessels in port-wine stains.[69]

Ablative Skin Resurfacing Treatments

Before the advent of such effective topical anesthetics (alone or in combination), ablative skin resurfacing procedures using carbon dioxide (CO_2) and erbium-doped YAG lasers often required the use of intravenous sedation. With the recent introduction of more-superficial ablative procedures and devices (including single-pass CO_2 and fractional laser and plasma skin resurfacing), the ability to obtain adequate intraoperative anesthesia with topical application of anesthetics has been achieved.[72–76] Because of the deeper dermal depths to which ablative lasers exert their action, topical lidocaine application times are generally lengthened to at least 60 minutes to enhance uniform anesthetic effect in the mid-to-deep dermis. Just before laser treatment, the anesthetic cream is completely removed and the skin dried so that laser-tissue interaction is unimpeded. Histologic assessment of CO_2 laser-treated skin demonstrated nonconfluent superficial damage after preoperative application of EMLA.[77] It was postulated that this translated into a better safety profile because EMLA's protective hydrating effect on the skin resulted in shallower CO_2 laser penetration depth.[77] Patient comfort during laser skin resurfacing can also be amplified by the additional use of a cooling device applied to the skin.[78] Despite these measures, oral sedation with a benzodiazepine, regional nerve blockade with infiltrative anesthesia, or intravenous anesthesia is often necessary during ablative laser procedures to achieve substantial pain relief.

Cosmetic Injectables

Although application of topical anesthetics is common before injection of dermal fillers, it is generally not necessary for botulinum toxin injection. The perioral region and palms and soles (for hyperhidrosis) are exceptions for which injection of botulinum toxin can cause considerable discomfort. Pretreatment with topical anesthetics before perioral botulinum toxin injection improves patient comfort, but the use of topical anesthesia before botulinum toxin injections on the palms and soles provides marginal anesthesia because of its impaired absorption through the thick stratum corneum.[79,80]

Patient discomfort during injection of a variety of filling agents is greatly minimized with the use of topical lidocaine-containing anesthetics. Many hyaluronic acid-containing products are now premixed with lidocaine, whereas other fillers are often reconstituted or mixed with lidocaine before injection. Although the need for concomitant topical anesthesia has been reduced, its application optimizes patient comfort during needle injections.

Chemical Peel

Application of topical anesthetics before chemical peeling has been shown to reduce discomfort without decreasing clinical efficacy of the peel. In a study assessing the use of topical anesthesia for peels, lidocaine was applied without occlusion for 30 minutes after a superficial unbuffered 70% glycolic acid peel and before a medium-depth 35%

trichloroacetic acid (TCA) peel. Although application of the topical anesthetic after the glycolic peel provided for its enhanced absorption for the more painful (TCA) portion of the procedure, the application of topical lidocaine did not affect the clinical and histopathologic outcome of the medium-depth TCA peel.[81] Caution is advised with this technique, because an inadvertently deep superficial chemical peel may disrupt the epidermal barrier and result in excessive anesthetic absorption.

Safety

No standard guidelines exist for optimal use and safety of all topical anesthetics. Practitioners should read the package inserts of individual products and be completely familiar with their unique characteristics. Suggestions on safe application relate to the size of the anatomic area to be applied, the age and weight of the patient, and the amount (in grams) of anesthetic to be applied. Unfortunately, guidelines do not explicitly stratify the recommended dosage based on the anatomic area to be treated. Absorption of anesthetic will occur more effectively over thin genital mucosal skin than on much thicker acral skin. Product inserts typically recommend the avoidance of application to oral mucosa and to the eyes to prevent severe ocular irritation.[56,57,82]

Many practitioners routinely exceed the recommended guidelines for safe application of different products. Improper or excessive use of topical anesthetics can have severe consequences, including death. Practitioners should take caution and be prepared to manage signs and symptoms of toxicity when using products in excess of published guidelines. Tables 1 and 2 provide helpful estimates to properly estimate the surface area of various anatomic locations in men and women. Topical anesthetic safety is predicated upon judicious use by practitioner and patient, and the percentile estimates created by the U.S. Environmental Protection Agency should reinforce the notion that covering whole limbs or even half of an entire torso during a single procedural session is potentially unsafe. For example, application of topical anesthetic to the entire thigh of an average female is approximately 1,600 cm^2 and would far surpass the recommended area of application proposed by product manufacturers. Table 5 may be used as a guide to facilitate safer use of topical anesthetics and increase patient comfort during office procedures.

The manufacturer of EMLA cites broad parameters to be monitored to avoid systemic toxicity when the cream is applied to patients with intact skin who have normal renal and hepatic function. As

TABLE 5. Tips for Optimal Topical Anesthetic Use and Increasing Patient Comfort

Apply topical anesthetic only on intact skin (avoid inflamed, denuded, eroded, or eczematous areas)
Avoid contact of anesthesia to the eye mucosa to prevent ocular injury
Avoid use of amide topical anesthetics in patients with hepatic failure
Limit eutectic mixture of local anesthetics use in newborns, particularly those taking methemoglobinemia-inducing agents
Be mindful of product amount applied, total surface area covered, thickness of stratum corneum, and duration of application
For large treatment areas, limit product application to select areas ("hot spots") that are most sensitive and forgo application of topical anesthetic to less sensitive areas
Supplement topical anesthesia with oral anxiolytics, pain relievers, nerve blocks, direct local anesthesia, and intravenous sedation as appropriate
Facilitate procedure ease with pretreatment over-the-counter or prescription analgesics
Apply ice, refrigerated ultrasound gels, and air cooling devices (e.g., Zimmer) during treatments to increase patient comfort and decrease or eliminate the use of topical anesthetic
Use patient distraction strategies such as talking to the patient ("talkesthesia"), deep breathing exercises, and stress-squeezing balls to facilitate comfort during procedures

an example, patients older than 7 years who weigh more than 20 kg should have no more than 20 g of EMLA applied to their skin and covering no more than 200 cm^2 of surface area for less than 4 hour. On the other hand, newborns younger than 3 months of age weighing less than 5 kg should have no more than 1 g of EMLA applied to an area no larger than 10 cm^2 and for less than 1 hour. There appears to be a significant therapeutic safety window for EMLA because peak blood levels of anesthetic after a 60-g application to 400 cm^2 for 3 hours are 0.05 to 0.16 μg/mL for lidocaine and 0.02 to 0.10 μg/mL for prilocaine. Toxic levels of lidocaine and prilocaine are greater than 5 and 6 μg/mL, respectively. For a more-extensive summary of these guidelines, see Table 6 (EMLA product insert).

The manufacturer of LMX notes that 1 g of cream equates to 5 cm of cream squeezed from the tube. They recommend that, in adults (including elderly adults and children aged 1 month and older), 1 to 2.5 g of cream be applied to cover a 6.25-cm^2 area of skin when used for venous cannulation. No more than 1 g of cream should be applied to infants younger than 1 year. LMX-4 should not be applied to an area larger than 100 cm^2 for patients weighing less than 10 kg and an area greater than 600 cm^2 for patients weighing 10 to 20 kg.[83] Some have recommended that the total dose of a topical anesthetic should be less than the dose for an infiltrative anesthetic at any site.[84]

Use of the lidocaine–tetracaine patch does not result in appreciable plasma levels of anesthetic. Application of one patch to intact adult skin for 30 minutes produced a peak plasma lidocaine concentration of 1.7 ng/mL, and tetracaine levels were undetectable. Simultaneous and sequential application of multiple patches in children for less than 30 minutes and adults for less than 60 minutes produced plasma levels well below that associated with serious toxicity (Synera product insert). Caution is still advised for anesthetic patch use on broken or inflamed skin because higher plasma levels of lidocaine and tetracaine can result.

Management of Toxicity

Rapid recognition of anesthetic toxicity is the most important step in managing an overdose. Once it is suspected that a patient is experiencing any of the aforementioned signs or symptoms, the topical anesthetic must be immediately washed off. The patient should be placed in a supine position and vital signs taken. If the patient has lost consciousness, maintenance of a patent airway and ventilation are paramount. Benzodiazepines may be administered, and serum lidocaine levels should be checked. Anticonvulsants should be provided as prophylaxis or to treat seizures induced from anesthesia toxicity.

Conclusion

Practitioners are increasingly using topical anesthetics to decrease the pain associated with superficial dermatologic, aesthetic, and laser procedures. Lidocaine-containing products play an integral role by providing patient comfort with minimal side effects. Careful attention must be paid to the particular anatomic location, the total

TABLE 6. Recommended Maximum Dose and Application Area of Eutectic Mixture of Local Anesthetics (EMLA; product insert)

Age and Body Weight Requirement	*Maximum Total Dose of EMLA Cream, g*	*Maximum Application Area, cm^2*	*Maximum Application Time, Hours*
0–3 months or <5 kg	1	10	1
3–12 months and >5 kg	2	20	4
1–6 years old and >10 kg	10	100	4
7–12 years old and >20 kg	20	200	4

surface area covered, and the duration of anesthetic skin contact. Many case reports document adverse outcomes associated with the use of compounded non-FDA-approved products that have inappropriately high anesthetic concentrations and from the use of topical anesthetics on excessively large skin surface areas during laser treatments. Careful selection and application of topical anesthetics can decrease or eliminate pain during many cutaneous procedures, reduce anatomic distortion by minimizing volume of intradermal local anesthesia, and decrease anxiety in patients who fear pain from procedures.

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